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Mirror neuron system activation in children with developmental coordination disorder: A replication functional MRI study

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Abstract

Background: It has been hypothesised that abnormal functioning of the mirror neuron system (MNS) may lead to deficits in imitation and the internal representation of movement, potentially contributing to the motor impairments associated with developmental coordination disorder (DCD).

Aims: Using fMRI, this study examined brain activation patterns in children with and without DCD on a finger adduction/abduction task during four MNS activation states: observation; motor imagery; execution; and imitation.

Methods and Procedures: Nineteen boys (8.25 – 12.75 years) participated, including 10 children with DCD (≤16th percentile on MABC-2; no ADHD/ASD), and nine typically developing controls (≥25th percentile on MABC-2).

Outcomes and Results: Even though children with DCD displayed deficits behaviourally on imitation (Sensory Integration & Praxis Test Subtests) and motor imagery assessments prior to scanning, no differences in MNS activation were seen between the DCD and control groups at a neurological level, with both groups activating mirror regions effectively across conditions. Small clusters of decreased activation during imitation were identified in non-mirror regions in the DCD group, including the thalamus, caudate, and posterior cingulate - regions involved in motor planning and attentional processes.

Conclusions and Implications: The results of this study do not provide support for the MNS dysfunction theory as a possible causal mechanism for DCD. Further research to explore attentional and motor planning processes and how they may interact at a network level may enhance our understanding of this complex disorder.

What this paper adds

Developmental coordination disorder (DCD) is a condition characterised by an inability to perform fine motor (hand writing and shoelace tying) and gross motor skills (playing sport and getting dressed) at an age appropriate level (American Psychiatric Association, 2013). Although neuroimaging in this population is an expanding area of research, limited exploration has been undertaken to explore the mechanisms of this disorder at a neurological level. This study further explored the hypothesis that abnormal functioning of the mirror neuron system (MNS) may contribute to the motor impairments associated with developmental coordination disorder (DCD). These findings contribute to, and extend, the small body of functional neuroimaging studies in this population. Given that children with DCD and controls displayed similar activation profiles in MNS regions, it is likely that the imitation and motor imagery performance deficits observed behaviourally in children with DCD stem from dysfunction of other neural networks also supporting these processes. This research provides new information about the underlying mechanisms of the motor deficits characteristic of DCD, with the findings pointing to deficits in neural areas linked to motor planning and attention.

Keywords

Developmental Coordination Disorder; DCD; Mirror Neuron System; Imitation; Motor Imagery; Functional Magnetic Resonance Imaging; fMRI

Highlights

Children with DCD had reduced imitation and motor imagery performance

Children with and without DCD activated MNS regions

No group differences in MNS activation were identified

Small group differences were found in motor planning and attention brain regions

1. Introduction

Learning via imitation and through the internal representation of movement is thought to be one of our primary modalities of learning and consolidating new motor skills. The mirror neuron system (MNS) is a fronto-parietal network of multimodal neurons in the central nervous system that has an integrative role in these processes, firing when a person observes, imagines, executes, and imitates actions (Decety, 1996; Iacoboni & Dapretto, 2006). This network has recently been hypothesised to contribute to the motor impairments that are characteristic of developmental coordination disorder (DCD) (Licari et al., 2015; Reynolds, Licari, Billington, et al., 2015; Reynolds, Thornton, et al., 2015; Werner, Cermak, & Aziz-Zadeh, 2012). Deficits in imitation (Elbasan, Kayıhan, & Duzgun, 2012; Reynolds, Kerrigan, Elliott, Lay, & Licari, 2016; Sinani, Sugden, & Hill, 2011; Zoia, Pelamatti, Cuttini, Casotto, & Scabar, 2002) and motor imagery performance (Adams, Lust, Wilson, & Steenbergen, 2014; Reynolds, Licari, Elliott, Lay, & Williams, 2015) in children with DCD have been used to support this hypothesis. To extend our knowledge of this system, further research is required to increase our understanding of the functioning of this system at a neurological level (Reynolds, Licari, Billington, et al., 2015; Reynolds, Thornton, et al., 2015). Functional activation differences in mirror neuron regions may underlie the motor, imitation, and motor imagery impairments, and contribute to the movement difficulties characteristic of children with DCD.

The MNS circuit in humans is believed to incorporate the pars opercularis (BA44) of the inferior frontal gyrus (IFG; Kilner, Friston, & Frith, 2007), the adjacent ventral premotor cortex (PMv; BA6; Buccino et al., 2001; Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Rizzolatti et al., 1996) and the rostral inferior parietal lobule (IPL; BA 39 and 40; Arbib, Billard, Iacoboni, & Oztop, 2000; Caspers, Zilles, Laird, & Eickhoff, 2010; Rizzolatti & Craighero, 2004; Figure 1). These mirror regions fire when one actively observes, imagines, executes, or imitates a movement, with a progressive increase in functional MRI (fMRI) blood-oxygen-level dependent (BOLD) signal from observation through to imitation (Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni, 2006). Another important area involved in the MNS is the superior temporal sulcus (STS). Although STS neurons are not activated during motor execution (Aziz-Zadeh, Koski, et al., 2006; Buccino, Solodkin, & Small, 2006), this area is thought to be connected with mirror regions via the arcuate fasciculus and parallel tracts (Catani, Jones, & ffytche, 2005; Iacoboni et al., 1999; Rizzolatti,

Fogassi, & Gallese, 2001) and is believed to play an important role in visual input during observation by coding for goal-directed and meaningful actions (Jellema, Baker, Wicker, & Perrett, 2000; Perrett et al., 1989). The human MNS has been proposed to represent a 'dynamic feedback control system' (Schippers & Keysers, 2011, p. 40) that supports both forward and inverse internal modelling processes, with a primary predictive control function (Figure 1).

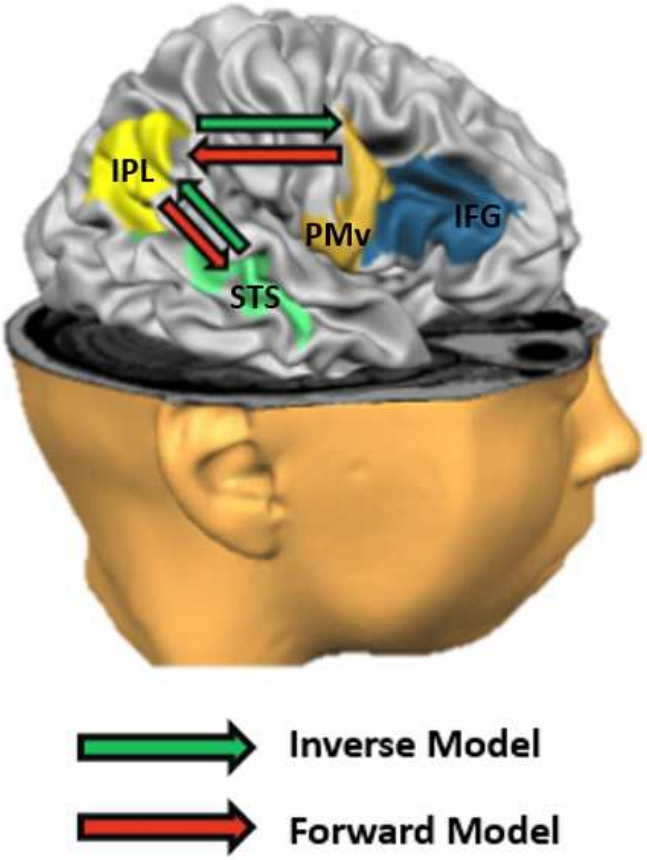

Figure 1. Information flow in the mirror neuron system (STS: superior temporal sulcus, IPL: inferior parietal lobule, PMv: ventral premotor cortex, IFG: inferior frontal gyrus; (created using images from BrainVoyager Brain Tutor: http://www.brainvoyager.com/products/braintutor.html; Goebel, Esposito, & Formisano, 2006).

At a behavioural level, research exploring deficits in imitation and motor imagery performance has been used as evidence to support the MNS dysfunction hypothesis of DCD (Reynolds, Thornton, et al., 2015; Werner et al., 2012). Imitation provides a foundation for skill learning via observation and is an important mechanism from a young age (Arbib et al., 2000; Billard & Arbib,

2002). The use of motor imagery, on its own, and in conjunction with traditional motor execution training, has repeatedly been shown to improve motor skill performance (Buccino et al., 2006) and assist motor skill development and acquisition (Decety, 1996). Imitation of learned, meaningful skills (Dewey, 1993; Sinani et al., 2011; Zoia et al., 2002) and non-meaningful simple and complex gestures (Elbasan et al., 2012; Goyen, Lui, & Hummell, 2011; Reynolds et al., 2016) have been shown to be performed poorly by children with DCD, who make more errors and respond slower to visual cues. In addition to imitation deficits, children with DCD have difficulty with motor imagery. Results on mental rotation and other motor imagery tasks suggest that children with DCD are able to adopt the use of a motor imagery strategy; however, they make slower, less accurate responses to stimuli (Adams et al., 2014, 2017; Fuelscher et al., 2016; Reynolds, Thornton, et al., 2015).

In addition to the behavioural evidence, some support for MNS dysfunction is evident in the small body of fMRI research in this population (Debrabant, Gheysen, Caeyenberghs, Van Waelvelde, & Vingerhoets, 2013; Kashiwagi, Iwaki, Narumi, Tamai, & Suzuki, 2009; Licari et al., 2015; Zwicker, Missiuna, Harris, & Boyd, 2010, 2011). Although not directly exploring MNS function, these studies have identified differences in activation patterns, and functional (McLeod, Langevin, Goodyear, & Dewey, 2014, 2016) and effective (Querne et al., 2008) connectivity of cortical areas linked to the MNS, using a range of tasks and resting state paradigms. The strongest initial evidence for possible MNS dysfunction comes from a recent fMRI study conducted by Licari et al. (2015), who found that during the imitation of a finger sequence task, children with DCD had decreased activation in the left IFG compared to controls. Hypothesised to possibly reflect MNS dysfunction, a follow up study was undertaken to specifically explore MNS functioning during observation, execution, and imitation of the same finger sequencing task (Reynolds, Licari, Billington, et al., 2015). The control group was found to have significantly greater activation than the DCD group during observation in the pars opercularis of the IFG, the precentral gyrus, middle temporal gyrus, posterior cingulate, and precuneus (Reynolds, Licari, Billington, et al., 2015). In addition, an interaction effect between group and task condition was seen in the pars opercularis, a key MNS region, with the DCD group showing a large deactivation in this region during imitation compared to the other conditions (Reynolds, Licari, Billington, et al., 2015). Although suggested to provide preliminary evidence for MNS dysfunction, and children with DCD possibly

adopting different neural strategies while performing the different task conditions, the lack of expected MNS signal increase from execution to imitation at a whole brain level was interpreted as a potential learning effect, whereby the extent of activation of MNS regions was likely reduced, which may have prevented group differences during execution and imitation from being identified.

Further research to explore hypothesised MNS dysfunction using simple target-directed finger movements without practice prior to scanning to circumvent the possible effect of motor learning, and to incorporate motor imagery into the fMRI task paradigm is required (Reynolds, Licari, Billington, et al., 2015). Therefore, the present study aimed to use fMRI to investigate whether a deficit in the MNS exists in children with DCD by examining brain activations during the performance of a target-directed adduction/abduction finger tapping task (modified from: Aziz-Zadeh, Koski, et al., 2006; Aziz-Zadeh, Maeda, Zaidel, Mazziotta, & Iacoboni, 2002) under four conditions: (1) action observation; (2) motor imagery; (3) action execution; and (4) imitation. (Aziz-Zadeh, Koski, et al., 2006; Decety, 1996; Iacoboni et al., 1999). It was hypothesized that there would be decreased activation in the MNS of children with DCD compared to controls, specifically in the pars opercularis of the IFG, the PMv, IPL and STS, most prominent during the imitation condition. In addition, this study also aimed to explore other cortical areas that may contribute to the movement difficulties seen in children with DCD.

2. Methods

2.1 Participants

Thirty-one right-handed males, aged 8 to 13 years participated in this cross-sectional research study. Of these participants, 12 (six DCD, six control) were subsequently excluded: three were withdrawn prior to the completion of scanning due to movement (three DCD), six during the analysis stage due to excessive movement (1 DCD; 3 control) and signal dropout (one DCD; one control), and three due to neurological abnormalities (one DCD; two control; confirmed by a neuroradiologist). This left a final sample of 19 males (10 DCD; nine control). Group 1 consisted of 10 males with DCD ($\leq 16^{th}$ percentile Movement Assessment Battery for Children – 2nd edition; MABC-2; Criterion A), recruited from the University of Western Australia (UWA) Paediatric Exercise Programmes, and clinical referrals, who met the four DSM-5 diagnostic criteria for DCD (APA, 2013). Parental interview confirmed the movement difficulties impacted activities of daily

living (Criterion B), that onset was early in the developmental period (Criterion C), and that there was no other condition that may better explain the movement difficulties (Criterion D). Group 2 consisted of 9 group age-matched typically developing controls (≥25th percentile MABC-2) recruited from the local community. Only right-handed males were recruited to eliminate any potential lateralisation or gender differences that may exist in brain activation patterns (Cheng, Tzeng, Decety, Imada, & Hsieh, 2006), imitation (Chipman & Hampson, 2007) or motor imagery ability. Ethics approval was obtained from the Human Research Ethics Committee (RA/4/1/6492) at UWA. Written consent was obtained from parents and participants prior to the commencement of the study and ongoing verbal assent was sought from participants throughout each phase of the study. Rolling recruitment and data collection ran from August 2014 to June 2016.

2.2 Experimental design and screening assessments

Participants were required to attend two testing sessions. During the first session, participants completed motor and diagnostic screening assessments to ensure that they met the diagnostic criteria for inclusion. Motor proficiency was assessed using the MABC-2 (Henderson, Sugden, & Barnett, 2007). Due to the high level of comorbidity of DCD with other neurodevelopmental disorders (Dapretto et al., 2006), children with a diagnosis of either autism spectrum disorder (ASD), or attention deficit hyperactivity disorder (ADHD), or any neurological conditions (Criterion D) were excluded from the study. In addition, the Childhood Autism Rating Scale (CARS; Saemundsen, Magnusson, Smari, & Sigurdardottir, 2003; Schopler, Reichler, & Renner, 1988) and the Swanson, Nolan and Pelham-IV (SNAP-IV) ADHD questionnaire (Bussing et al., 2008) were used to assess symptoms of ASD and ADHD. Handedness was screened using a child modified version of the Edinburgh Handedness Inventory (Oldfield, 1971), and only right-handers (score ≥ 40) were included to eliminate any potential brain lateralisation differences related to handedness.

Once it was established that children met the inclusion criteria, imitation and motor imagery assessments were undertaken to explore MNS function at the behavioural level. The Postural Praxis (whole body imitation) and Sequencing Praxis (hand and finger sequencing imitation) sub-tests from the Sensory Integration and Praxis Tests (SIPT) developed by Ayres and colleagues (Ayres, 1989) were used to assess participants' imitative ability. Motor imagery proficiency was

assessed using a complex hand rotation task (Butson, Hyde, Steenbergen, & Williams, 2014; Hyde et al., 2014; Reynolds, Licari, Elliott, et al., 2015), with response time and accuracy measures recorded. Eighty hand stimuli were presented in two rotational axes (palm/back) and eight 45° rotational steps (for more information on task, see Reynolds, Licari, Elliott, et al., 2015). Speed and accuracy performance measures conformed to biomechanical constraints, suggesting that children used a motor imagery strategy to perform the task. During this session, participants also completed fMRI familiarisation during which they were introduced to the scanning environment (noise, confined space, head coil and restraints), and were provided with skills to enable them to lie still for a readable scan. This familiarization protocol has been used successfully in previous research by researchers involved in this study (Licari et al., 2015; Reynolds, Licari, Billington, et al., 2015). Participants were also familiarized with the task conditions. Due to previous research indicating that a learning effect may have occurred as a result of practicing the task prior to scanning (Reynolds, Licari, Billington, et al., 2015), an alternate hand clenching task was used to practice the different conditions and cues involved in this study. The second session involved the use of fMRI to examine differential brain activations as children performed an adduction/abduction finger tapping task. Participants were shown the task immediately prior to their scan to avoid a learning effect. This session was conducted at the Department of Radiology at Sir Charles Gairdner Hospital, Western Australia.

2.3 Imaging parameters

Imaging was conducted using a Philips Ingenia 3T Multi Transmit Wide Bore Scanner, with participants wearing a 12-channel head coil. The participants' head was restrained with soft pads to prevent small, unwanted movements from causing artefacts. A strap was used to help immobilize both wrists and forearms to limit the movement of the active hand in order to minimize participant head movement during scanning. A thermo-plastic splint was worn by participants on the active dominant hand during scanning to isolate movement in the digits. High-resolution anatomical images were acquired first (T1-weighted 3D FFE 175 slices 1 × 1 × 1 mm), followed by two eight minute functional studies (T2-weighted gradient echo, TR/TE = 3000/35 ms, flip angle 90°, 25 axial slices with a thickness of 4 mm, interslice gap = 0 mm, in-plane resolution 1.8mm×1.8 mm). Total scan time was 22.5 min.

2.4 Scanning task

Participants performed a target-directed adduction/abduction (side to side) index finger tapping task (modified from previous mirror neuron research: Aziz-Zadeh, Koski, et al., 2006; Aziz-Zadeh et al., 2002; Figure 2) using their right hand under four separate conditions: (1) action observation; (2) motor imagery; (3) action execution; and (4) action imitation. During action observation, participants viewed the finger tapping task and were prompted with a red coloured circle to observe the task but not imagine or execute it. In the motor imagery condition, participants were prompted by a yellow coloured circle to imagine themselves perform the finger tapping task with a still shot of the first hand stimulus image on the screen. In the action execution condition, participants were prompted by a green coloured circle to perform the finger tapping task with a still shot of the first hand stimulus image on the screen. Lastly, in the action imitation condition, participants viewed the sequencing task and were prompted with a green coloured circle to imitate the finger actions as they observed them. All images were displayed from a first person point of view, with a metronome tick (1 Hz) used as an auditory cue to coordinate the timing of movements performed in each condition. The task was demonstrated to participants outside the MRI room, on a laptop immediately prior to scanning.

Participants completed a total of eight repetitions of each condition in a randomized order across two functional block design scans (four presentations per scan). Each condition lasted for approximately 18 seconds with 12 seconds of rest (rest condition) between each to allow for the BOLD response to return to baseline. The rest condition was a non-mirror neuron observation task to isolate changes in brain responses to those evoked by the task; participants viewed two scrambled hand images with a red cross, which were designed to have a similar contrast and luminance in the center of the screen to the active condition images (modified version of: Aziz-Zadeh, Iacoboni, & Zaidel, 2006). A smoothing function was applied to the edges of the scrambled blocks to remove the sharp edges. Rest images also changed at a frequency of 1Hz along with a metronome tick. An assessor in the scan room observed the performance of tasks within the scanner to ensure tasks were completed correctly, however, no quantitative measures were recorded. In addition, participants were asked whether they were imagining performing the task for the imagery condition.

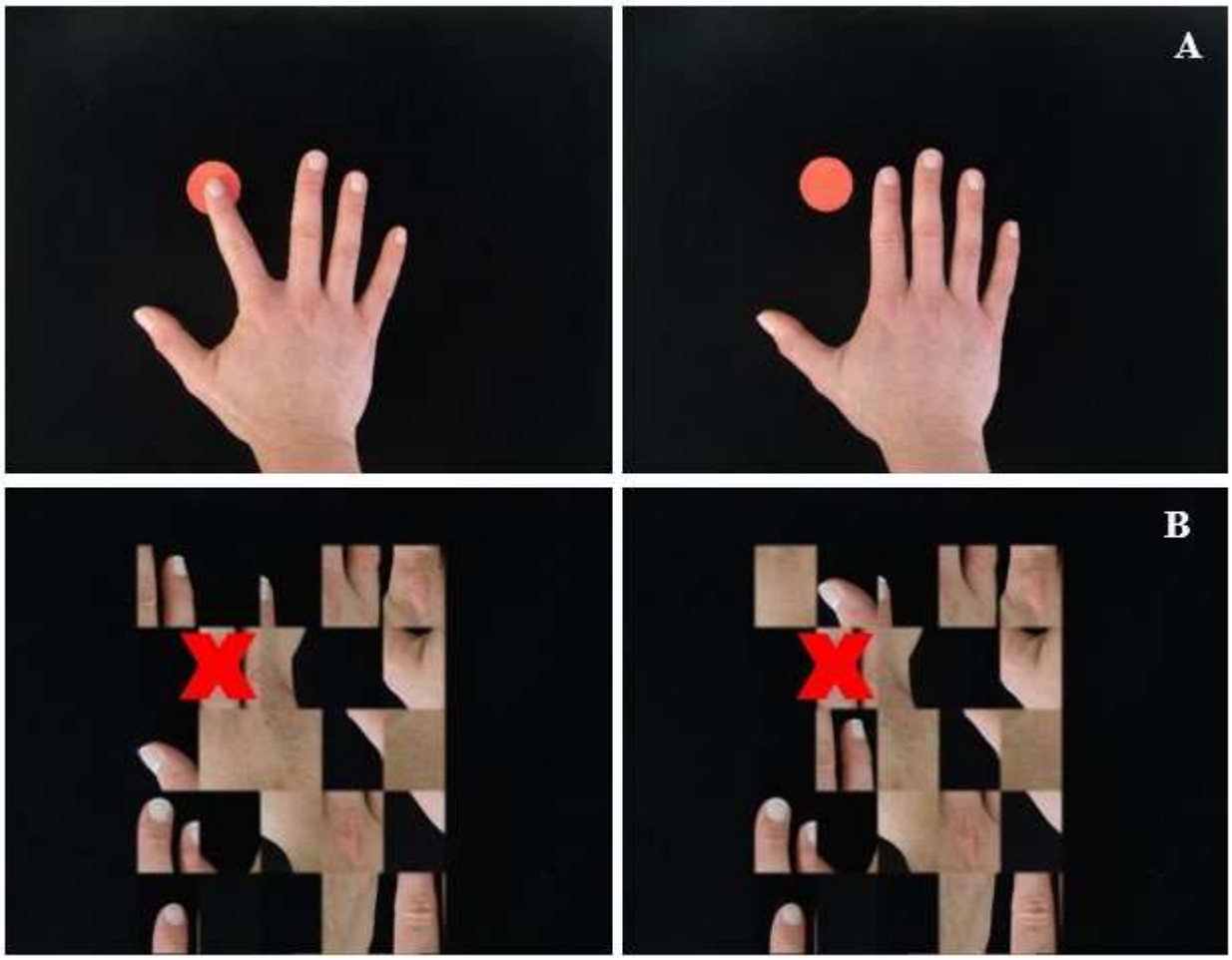

Figure 2. A: Adduction/abduction finger tapping task condition images (observation example), B: Rest condition images.

2.5 Imaging analysis: Functional

All fMRI data processing and whole brain analysis was carried out using SPM12 software (Wellcome Department of Cognitive Neurology, London). Prior to analysis, all images were corrected for slice timing using the middle slice as a reference slice. Structural anatomical scans were placed into AC-PC space, and all structural and functional images reoriented accordingly. A stringent fourth degree b-splice interpolation realignment procedure was applied to the images to realign to a mean functional image. In-scanner motion was checked for each participant, four participants (one DCD; three control) were removed at this stage for displaying motion > 3 mm. All other participants displayed minimal motion and there was no apparent difference of in scanner head movement between the DCD and control groups. The mean functional image created during

realignment (source image), and all realigned functional images (other images) were co-registered to the structural image (reference image). Segmentation using SPM12 tissue probability maps was performed to segment the anatomical images into grey matter, white matter and cerebrospinal fluid. All structural and functional images were normalized using affine and smooth non-linear transformations to an EPI template in Montreal Neurological Institute (MNI) space. Finally, all images were smoothed with a full width half maximum Gaussian kernel of 8 mm to optimise functional registration of activations.

Each run was split into blocks to reflect the observation, motor imagery, execution, and imitation task conditions outlined above. Individual statistical contrasts were set up by using the general linear model to fit each voxel with a combination of functions derived by convolving the standard hemodynamic response with the time series of the events and removing low-frequency noise with a high-pass filter with a frequency cut off of 128 s (Friston et al., 2000). The six nuisance regressors capturing head motion from each session that were created for each participant during the realignment stage were built into the first level models as covariates. In order to examine the signal activation patterns of the MNS, the main effect of each individual condition (e.g., observation, motor imagery, execution, and imitation) was contrasted against the rest condition (to identify brain regions activated by each task condition) using exploratory whole brain analysis. Contrasts were run at a cluster corrected level, with voxel height thresholds set at $p < 0.001$ (uncorrected), with an additional extent threshold set for each contrast to correct for multiple comparisons, thus activations passed a cluster-level extent threshold of $p < 0.05$ (FWE corrected; Friston, Holmes, Poline, Price, & Frith, 1996; Nichols & Wilke, 2012). Second level between-group contrasts (control > DCD; DCD > control) were performed for each condition, first at a cluster corrected level of $p_{FWE} < 0.05$. Where no activation differences were identified at a corrected level, contrasts were re-run at an uncorrected level of $p < 0.001$. All significant clusters extracted in MNI coordinates were converted to Talairach coordinates; the nearest grey matter structure, and Brodmann area were identified using Talairach Client (http://www.talairach.org/; Lancaster et al., 1997; Lancaster et al., 2000) and the Co-Planar Stereotaxic Atlas of the Human Brain (Talairach & Tournoux, 1988).

Region of interest (ROI) analysis was also conducted in pre-selected locations to explore signal patterns in MNS regions. Percent signal change values were extracted from 15 ROIs created in MarsBaR region of interest toolbox for SPM (MarsBaR: http://marsbar.sourceforge.net/; Brett, Anton, Valabregue, & Poline, 2002) in SPM8. Following Reynolds and colleagues (Reynolds, Licari, Billington, et al., 2015), each ROI consisted of a 10mm diameter sphere, centered on the coordinates reported in the study by Aziz-Zadeh et al. (Aziz-Zadeh, Koski, et al., 2006). This included mirror regions in the pars opercularis of the IFG (BA44: x=-47 y=8, z=6; x=44, y=8, z=21; x=-36, y=14, z=24), supplementary (BA6: x=12, y=2, z=66; x=1, y=6, z=52) and premotor areas (BA6: x=-32, y=2, z=58; x=-42, y=0, z=48; x=36, y=-4, z=56; x=38, y=0.3, z=54; x=41, y=-1, z=38; x=-30; y=-5; z=60; x=-16; y=0; z=64), inferior /posterior parietal lobe (BA40: x=-56, y=-26, z=36; x=52, y=-30, z=38), and STS (BA21: x=-56, y=-58, z=6). A series of 2×4 mixed ANOVAs were run for each ROI on the percent signal change values extracted from individual participants. As a result of the lack of anatomical maps in children and similar functional data, the ROI analysis was based on established coordinates from adult MNS data (Aziz-Zadeh, Koski, et al., 2006). Although adults do not map on to children perfectly, it was felt that this approach was more accurate and objective than the use of anatomical ROIs.

3. Results

The final sample consisted of 19 participants (10 DCD; nine controls). The characteristics of this group are presented in Table 1. Groups were well matched for age, with no significant difference identified between the DCD (8.25 – 12.75 years) and control groups (8.33 – 12.25 years). By inclusion criteria of the groups, children with DCD had significantly poorer motor proficiency compared to the controls on the MABC-2 ($p < 0.001$), with the DCD group ranging from the 1st – 16th percentiles, and controls from the 37th – 98th percentiles. Consistent with previous research (Reynolds, Licari, Billington, et al., 2015), children with DCD displayed significantly more ADHD and autistic symptoms ($p < 0.05$), however, none of the children with DCD had a formal diagnosis of either disorder. Both questionnaires include questions about engagement in movement related activities, which is likely, in part, to explain these group differences. Children with DCD were found to have significantly decreased imitative ability as compared to the control group on both the postural and sequencing praxis, and reduced accuracy levels for the motor imagery task ($p < 0.05$).

Table 1. Participant characteristics for fMRI study (DCD and typically developing peers).

	DCD (N=10)		TD (N=9)		t/*U*	*p*	*d*
	Mean/ Median	SD/ IQR	Mean/ Median	SD/ IQR			
Age (years) [a]	10.18	1.34	10.41	1.17	0.401	0.694	0.18
MABC-2 (percentile)	7.80	5.40	70.11	23.04	7.922	<0.001**	3.72
CARS[a]	17.90	2.18	15.22	0.36	2.964	0.009*	1.57
SNAP-IV[a]	0.87	0.53	0.31	0.22	3.820	0.004*	1.33
Postural Praxis[a]	23.30	4.14	28.11	2.80	2.931	0.009*	1.36
Sequencing Praxis[a]	84.50	9.28	98.56	6.34	3.805	0.001*	1.77
MI combined accuracy[b]	87.76	74.91-93.12	95.00	93.12-98.12	15.000	0.014*	-

3.1 fMRI whole brain analysis: Condition contrasts

To explore MNS activation patterns, and whether there was a characteristic progressive increase in BOLD signal across conditions from action observation, motor imagery, action execution, to imitation (Aziz-Zadeh, Koski, et al., 2006; Iacoboni et al., 1999) during the finger adduction/abduction task, the main effect of each individual condition was contrasted against rest. The groups were initially collapsed to identify whether cortical areas typically associated with the MNS were activated across conditions. During the observation condition, there were no significant activation clusters compared to the rest condition (visual non-mirror control task). When children imagined themselves performing the task in the action imagery condition (purple in Figure 3), significant clusters of activation were found in the inferior-, middle-, medial-, and superior frontal gyri, supramarginal gyrus, posterior cingulate, and precuneus. All children reported that they imagined performing the finger tapping task. Furthermore, when children performed the task in the action execution (dark blue in Figure 3) and imitation (green in Figure 3) conditions, significant activation clusters were identified in the precentral gyrus and medial frontal gyrus, pre- and postcentral gyrus, inferior parietal lobule, thalamus, caudate and lentiform nucleus, with a greater extent of activation during imitation. The coordinates of the specific regions where significant activation was seen across the conditions are presented in Table 2.

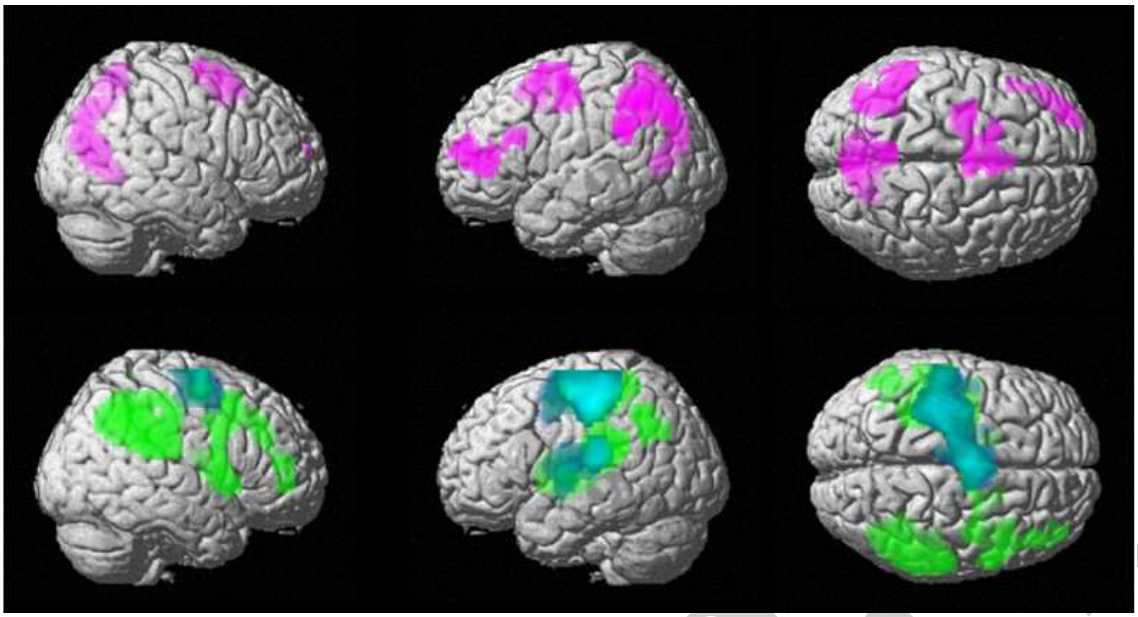

Figure 3. Main effect of observation > rest (N/A), motor imagery > rest (purple), execution > rest (dark blue), and imitation > rest (green). Cluster-level extent threshold of $p_{FWE} < 0.05$; (N.B. fading represents depth; sky blue/teal represents overlap of execution > rest and imitation > rest contrasts).

3.2 fMRI whole brain analysis: Group contrasts

When group differences were compared individually within each condition > rest, no significant differences were seen between groups in the action observation, motor imagery, or action execution conditions when run at corrected or uncorrected levels. However, in the imitation condition, children with DCD were found to have small clusters of decreased activation compared to controls in the right caudate, thalamus, posterior cingulate, middle frontal gyrus, and precuneus, and left thalamus (uncorrected $p < 0.001$; Table 3).

Group comparisons were also run for the imitation > execution, imitation > motor imagery, and imitation > observation contrasts, to explore regions that were more active when participants had to attend to and move in time with the visual stimuli, as opposed to just executing the movement without prompting visual stimuli, imagining without moving visual stimuli, or just watching the stimuli respectively. A number of uncorrected ($p < 0.001$) small clusters were identified in all three control > DCD contrasts (Table 4). There were no significant clusters for any of the DCD > control contrasts.

Table 2. Whole brain analysis: Condition comparison (cluster level correction, $p_{(FWE)} < 0.05$).

Anatomical region	Cluster (k)	Talairach coordinates			Brodmann area
		x	*y*	*z*	
Observation > Rest					
N/A					
Motor imagery > Rest					
Middle frontal gyrus (L)	903	-26	-7	50	6
Medial frontal gyrus (L)		-1	12	49	6
Superior frontal gyrus (L)		-14	9	60	6
Posterior cingulate (R)	1517	10	-66	13	30
Precuneus (L)		-6	-52	60	7
Precuneus (R)		3	-74	39	7
Inferior frontal gyrus (L)	344	-37	48	3	10
		-46	37	11	46
Superior frontal gyrus (L)		-26	58	14	10
Supramarginal gyrus (L)	722	-58	-39	30	40
Precuneus (L)		-38	-70	39	19
Inferior parietal lobule (L)		-44	-49	49	40
Execution > Rest					
Precentral gyrus (L)	2254	-40	-17	54	4
		-33	-21	51	4
Medial frontal gyrus (L)		-3	-5	54	6
Inferior parietal lobule (L)	330	-49	-24	18	40
Postcentral gyrus (L)		-49	-12	14	43
Thalamus (L)	476	-14	-19	10	Lateral posterior nucleus
Caudate (L)		-19	-12	21	Caudate body
Lentiform nucleus (L)		-22	-4	9	Putamen
Imitation > Rest					
Precentral gyrus (L)	3719	-40	-17	54	4
		-33	-21	51	4
Medial frontal gyrus (L)		-5	-5	50	6
Thalamus (L)	1542	-14	-19	7	Ventral posterior medial nucleus
Lentiform nucleus (L)		-19	-6	2	Lateral globus pallidus
Caudate (L)		-15	-8	17	Caudate body
Inferior parietal lobule (R)	1865	54	-34	29	40
		51	-47	45	40
		43	-50	49	40
Precentral gyrus (R)	803	59	9	9	44
		58	6	35	6
Superior frontal gyrus (R)		43	17	45	8
Supramarginal gyrus (L)	219	-54	-56	34	40
Inferior parietal lobule (L)		-47	-51	41	40
Angular gyrus (L)		-35	-58	38	39

Table 3. Between group analysis of task conditions > rest condition (uncorrected, $p < 0.001$).

Anatomical region	Cluster (k)	Talairach coordinates			Brodmann area
		x	*y*	*z*	
Imitation					
Control > DCD					
Caudate (R)	45	20	-19	21	Caudate body
Thalamus (L)	18	-14	-33	11	Pulvinar
Caudate (R)	10	13	24	8	Caudate body
Thalamus (R)	29	6	-33	7	Pulvinar
		10	-35	15	Pulvinar
Posterior cingulate (R)		15	-40	11	29

Table 4. Between group analysis of imitation > observation, imagery, and execution conditions (uncorrected, $p < 0.001$).

Anatomical region	Cluster (k)	Talairach coordinates			Brodmann area
		x	*y*	*z*	
Execution: Control > DCD					
Insula (R)	16	31	-35	15	13
Caudate (R)	32	11	23	8	Caudate body
Medial frontal gyrus (R)	12	10	-7	54	6
Thalamus (R)	31	13	-35	7	Pulvinar
		4	-34	4	Pulvinar
Insula (L)	16	-40	-31	18	13
Parahippocampal gyrus (L)	14	-14	-37	7	30
Medial Frontal gyrus (L)	15	-12	-17	58	6
Postcentral gyrus (L)	11	-42	-20	36	3
Motor imagery: Control > DCD					
Caudate (R)	39	10	19	8	Caudate body
Superior temporal gyrus (L)	27	-38	-30	14	41
Cingulate gyrus (L)	13	-8	-2	39	24
Thalamus (R)	11	24	-13	25	Thalamus
Caudate (L)	11	-19	14	12	Caudate body
Observation: Control > DCD					
Precuneus (L)	33	-12	-66	46	7
Cingulate gyrus (L)	38	-8	-29	33	23
Precuneus (R)	28	13	-59	45	7
		8	-67	42	7
Transverse temporal gyrus (L)	10	-35	-38	15	41

3.3 fMRI region of interest

Using ROI percentage signal change analysis, significant main effects for task condition were observed in mirror neuron regions with a trend for increasing signal activations across the conditions to imitation. Post-Hoc analyses revealed significant within-subject differences with greater activation during the motor imagery, execution and imitation conditions compared with the observation condition in the posterior parietal regions, premotor and supplementary motor areas, and greater activation for motor imagery compared to observation in the pars opercularis. A significant group difference was identified in the right posterior parietal/inferior parietal lobe (x = 52, y = -30, z = 38, BA40, F = 4.570; $p = 0.047$), with controls having increased activation across conditions, compared to the DCD group (mean difference = 0.085). No significant condition x group interactions were found.

4. Discussion

The present study examined brain areas that contribute to the movement difficulties experienced by children with DCD, specifically, proposed deficits in MNS function (Reynolds, Thornton, et al., 2015; Werner et al., 2012). At a behavioural level, children with DCD had reduced performance proficiency on both imitation and motor imagery tasks, demonstrating that the children with DCD included in this study had deficits supportive of the MNS dysfunction hypothesis at a behavioural level. Interestingly, no differences in MNS activation were seen between groups at a neurological level, with both groups activating mirror regions similarly across conditions. At a whole brain level, group comparisons of neural activation for each task condition over rest condition revealed minimal between-group differences, with small clusters of decreased activation seen in the DCD group in non-mirror regions including the thalamus, caudate, and posterior cingulate during the imitation condition. When the imitation condition was compared to the other conditions, the DCD group displayed decreased activation compared to controls in the bilateral medial frontal gyrus, insula, caudate, and precuneus, the left postcentral, parahippocampal, superior temporal, and transverse temporal gyri, and right thalamus. No DCD > control activation was identified for any contrast. The reduced activation in these regions suggest that the imitation and imagery deficits observed in children with DCD may in part stem from difficulties with the planning phase of movement production, and integration and updating of relevant visuospatial information rather than deficits in MNS function.

The design of this study was based on previous MNS research (Reynolds, Licari, Billington, et al., 2015), incorporating additional MNS activation states using a novel task without prior practice to examine MNS function. The activation profiles observed at a within-subject level revealed that both groups effectively activated MNS regions, including the inferior and medial frontal gyri, and inferior parietal lobule, as well as other expected motor regions. Furthermore, an examination of the percentage signal changes in the ROI analyses revealed the expected increase in signal activation trends across conditions. Although there were no significant activation clusters for the observation > rest contrast, which we would expect to see (Caspers et al., 2010), it is possible that the rest condition, which also incorporated moving images, activated some mirror regions. Despite this, based on the consistent MNS activation patterns observed during the other task conditions, and across the conditions at a ROI level, any group differences at a neurological level in this system impacting movement execution would still be expected to be identified. Furthermore, an examination of the percentage signal changes in the ROI analysis revealed the expected increased signal activation trends across conditions from observation to imitation (Aziz-Zadeh, Koski, et al., 2006), suggestive of mirror region activation during the tasks. The increasing activation at whole brain and ROI levels across the conditions suggests that a practice effect was not encountered as it may have been in previous research (Reynolds, Licari, Billington, et al., 2015). The similar activation patterns observed by both the DCD and control groups across most ROIs, suggests that both groups activated mirror neuron regions to perform the tasks, with no differences in MNS activation patterns to support a deficit in this system at a neurological level.

The absence of between-group differences in MNS activation at a whole brain level is consistent with the results from the previous fMRI research by our research group (Reynolds, Licari, Billington, et al., 2015). Given the evidence for MNS dysfunction in DCD at a behavioural level in conjunction with differences in MNS activation patterns during other functional tasks (Debrabant et al., 2013; Kashiwagi et al., 2009; Licari et al., 2015; Querne et al., 2008; Reynolds, Licari, Billington, et al., 2015; Zwicker et al., 2010, 2011), the minimal group differences in MNS activation had previously been hypothesized to be the result of a learning effect. Recent fMRI research by Kashuk and colleagues (2017) identified a number of small clusters of decreased activiation in adults with pDCD during a hand rotation task in the bilateral middle frontal gyrus,

448 left superior parietal lobe and lobule VI of the cerebellum. While the differences in results
449 compared to this study could be a result of differences in brain activation patterns associated with
450 implicit (e.g. hand rotation) compared to explicit (our task) imagery tasks (Hétu et al., 2013), it is
451 also possible that between group motor imagery brain activation differences may have been
452 evident in this study had a more diffiicult task been used. Interestingly, however, to date, aside
453 from work by Zwicker and colleagues (2010, 2011), minimal differences in brain activation
454 patterns between children with and without DCD have been observed using fMRI across a range
455 of tasks (Debrabant et al., 2013; Kashiwagi et al., 2009;; Licari et al., 2015; Reynolds, Licari,
456 Billington, et al., 2015).
457
458 Although no group differences were identified in regions associated with the MNS, during
459 imitation, children with DCD were found to have reduced activation in small clusters in the caudate
460 body, thalamus (pulvinar), and posterior cingulate, compared to controls. Children with DCD also
461 had small clusters of reduced activation for all of the imitation > execution, imagery, and
462 observations contrasts, where attention to a visual stimulus as well as attention to task performance
463 was required. Again, these clusters were identified in the thalamus and caudate, as well as in the
464 cingulate gyrus, precuneus, insula, superior temporal gyrus and medial frontal gyrus. Differential
465 activation patterns in these non-mirror regions are consistent with neural activation patterns that
466 have been associated with impaired imitation. For example, lesions centered on the caudate
467 nucleus and insular cortex, have been associated with disturbed finger position imitation
468 (Goldenberg & Karnath, 2006).
469
470 The small differences in activation of these regions also suggest that reduced levels of motor
471 planning, and visuospatial and motor attentional processes at a neural level may be involved in the
472 motor deficits seen in children with DCD. The caudate has been identified to be involved in
473 automated processes such as motor planning, execution of action schemas (Grahn, Parkinson, &
474 Owen, 2008), attentional processes (Berger & Posner, 2000), and interestingly, has been
475 implicated in other neurodevelopmental disorders which have a high incidence of associated
476 movement difficulties (Schrimsher, Billingsley, Jackson, & Moore, 2002). The pulvinar
477 (thalamus) has been implicated in selective visuospatial attention, as well as acting to relay
478 attentional feedback to the visual cortex (Cola, Gray, Seltzer, & Cusick, 1999; Desimone &

Duncan, 1995; Kowler, Anderson, Dosher, & Blaser, 1995; Saalmann, Pinsk, Wang, Li, & Kastner, 2012; Zhou, Schafer, & Desimone, 2016). Furthermore, increased levels of visual attention and motor control during imitation have been associated with hyperactivation in the posterior cingulate cortex (Hanawa et al., 2016; Zhang et al., 2016), an integrative centre (Pearson, Heilbronner, Barack, Hayden, & Platt, 2011) involved in both motor and attention processes, suggesting that children with DCD may have difficulty integrating relevant information at a neurological level. The precuneus is thought to influence a wide range of highly integrated tasks including visuo-spatial imagery, attention orientation, and self-processing adopting a first-person perspective (Cavanna & Trimble, 2006); decreased activation in imitation > observation contrast in DCD is consistent with proposed deficits mentally manipulating body schema (Reynolds, Licari, Elliott, et al., 2015). Reduced activation of these regions in children with DCD may suggest that deficits attending to stimuli, learning of automated movements, and the processing and updating of relevant information may contribute to the motor deficits seen in DCD.

Deficits in motor planning, generating internal models and the use of feedforward information have previously been hypothesized to underlie the movement difficulties characteristic of DCD (Adams et al., 2014). The small reduced activation clusters in planning and attention regions during imitation in children with DCD provide preliminary support for dysfunction of motor planning and attentional processes neurologically. Differential activation and connectivity patterns in motor planning and attention regions have also been identified in children with DCD in other fMRI and rsfMRI studies (Debrabant et al., 2013; McLeod et al., 2014; Querne et al., 2008; Zwicker et al., 2010). In addition, reduced grey matter volumes in motor planning and attention regions have been reported (Reynolds et al., 2017). Interestingly, research on other neurodevelopmental disorders with movement difficulties, such as ADHD, also implicates these neural regions and processes (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Schrimsher, et al., 2002). In conjunction with the high levels of comorbidity associated with DCD, the incorporation of combined comorbidity groups in neuroimaging research may be beneficial for future research.

While this study found no evidence to support the MNS theory of motor impairment, there are some limitations to our work to consider. Although the adduction/abduction finger tapping task has been shown to activate MNS regions in previous research, the task itself is relatively simple

due to task constraints within a scanning environment. Imagery of simple tasks has, however, been shown to activate cortical networks comparable to those activated during complex imagined tasks (Szameitat, Shen, & Sterr, 2007). Despite this, it is possible that group differences may have become more apparent with a more complex task (Kuhtz-Buschbeck et al., 2003); however, performing a complex unlearned task during scanning is likely to present a challenge for children with DCD, as well as those without. As the sample size is small, although comparable with other studies in this population, uncorrected statistics have been reported for group comparisons and should be interpreted with caution. Given the small sample size, the study may have been under-powered to detect MNS differences between groups. To keep scan time to a minimum, the volume was reduced and did not extend down to the cerebellum. This brain region has been implicated in DCD (Marien, Wackenier, De Surgeloose, De Deyn, & Verhoeven, 2010; Zwicker et al., 2010, 2011), however, as this study was specifically exploring MNS, a trade-off was made to instead increase the number of task presentations in the fMRI protocol.

5. Conclusions and future directions

At a behavioural level, children with DCD displayed deficits in imitation and motor imagery performance. Given that children with DCD and controls displayed similar activation profiles in MNS regions, it is likely that the performance deficits observed behaviourally stem from dysfunction of other neural networks also supporting these processes. Further research may be beneficial, as it is also possible that the task utilized was too simple to elicits between group differences in the activation of the MNS. This research provides new information about potential underlying mechanisms of DCD, with the findings pointing to deficits in neural areas linked to motor planning and attention. Further fMRI research, in particular the use of motor attention tasks, to explore likely deficits in motor planning and internal forward modeling, and attentional processes, appears to be a promising research direction to increase our understanding of the causal mechanisms of the movement difficulties associated with DCD and potential targeted treatments. Resting state fMRI and dynamic causal modelling to explore effective connectivity between brain regions also has the potential to shed further light on the connectivity of other networks such as the default mode network, salience network and dorsal attention network at rest, as well as during imitation and other movement tasks.

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