Mirror Neuron Activation in Children with Developmental Coordination Disorder: A Functional MRI Study

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Abstract

The aim of this study was to reveal cortical areas that may contribute to the movement difficulties seen in children with Developmental Coordination Disorder (DCD). Specifically, we hypothesized that there may be a deficit in the mirror neuron system (MNS), a neural system that responds to both performed and observed actions. Using functional MRI, 14 boys with DCD ($\bar{x}$ = 10.08 years ± 1.31, range = 7.83 - 11.58 years) and 12 typically developing controls ($\bar{x}$ = 10.10 years ± 1.15, range = 8.33– 12 years) were scanned observing, executing and imitating a finger sequencing task using their right hand. Cortical activations of mirror neuron regions, including posterior inferior frontal gyrus, ventral premotor cortex, anterior inferior parietal lobule and superior temporal sulcus were examined. Children with DCD had decreased cortical activation mirror neuron related regions, including the precentral gyrus and inferior frontal gyrus, as well as in the posterior cingulate and precuneus complex when observing the sequencing task. Region of interest analysis revealed lower activation in the pars opercularis, a primary MNS region, during imitation in the DCD group compared to controls. These findings provide some preliminary evidence to support a possible MNS dysfunction in children with DCD.

Keywords: developmental coordination disorder (DCD); imitation; mirror neuron system (MNS); functional magnetic resonance imaging (fMRI); cortical function

1. Introduction

Development Coordination Disorder (DCD) is a neurodevelopmental condition characterized by impaired motor coordination that significantly interferes with an individual's academic achievement and performance of daily activities (American Psychiatric Association [APA] 2013; Cermak et al. 2002). It is the most prevalent childhood movement disorder affecting about 6% of children (World Health Organisation 2010; APA 2013). Individuals with DCD present with a wide spectrum of difficulties including poor fine and gross motor skills (such as dressing, tying shoelaces, handwriting and playing sports), (Zwicker et al. 2009, Zwicker et al. 2011) balance, and postural control (Geuze 2005). More recently, deficits in imitation ability (Dewey 1993; Elbasan et al. 2012; Goyen et al. 2011; Sinani et al. 2011; Zoia et al. 2002) have been highlighted. The etiology of DCD is currently unknown but it is generally thought to be related to a deficit in the functioning of the central nervous system (CNS) (APA 2013; Flouris et al. 2005; Steinman et al. 2010; Zwicker et al. 2009). A relatively new neural model to be implicated in DCD relates to a potential deficit in the functioning of the mirror neuron system (MNS) (Licari et al. 2015; Reynolds et al., in press; Steinman et al. 2010; Werner et al. 2012), a fronto-parietal network of brain regions playing an integrative role in imitation of motor skills. Due to its essential role in mediating imitation (Heiser et al. 2003), and its role in visual motor learning (Cross et al. 2006, 2009), dysfunction of the MNS has the potential to impact on the formation of motor representations and learning of new skills.

Mirror neurons were first discovered using single cell recordings, in a sector (area F5) of a macaque monkey's ventral premotor cortex (di Pellegrino et al. 1992, Fogassi and Gallese 2002; Gallese et al. 1996) and subsequently within the prefrontal cortex (Gallese et al. 2002). Numerous neurophysiological and brain imaging studies have provided indirect evidence that the MNS also exists in humans, with similar but possibly more evolved properties. The MNS in humans is thought to be critical for imitation (Heiser et al., 2003, Iacoboni 2005; Iacoboni et al. 1999). The homologous MNS areas in the human brain are thought to constitute the pars opercularis of the inferior frontal gyrus (IFG; Brodmann's area, BA 44) (Petrides and Pandya 1994), ventral premotor cortex (Buccino et al. 2001; Grafton et al. 1996; Rizzolatti et al. 1996b; Rizzolatti and Craighero 2004), and inferior parietal lobule (Arbib et al. 2000; Rizzolatti and Craighero 2004; Rizzolatti and Matelli 2003) (see Fig. 1). Also playing an important role in the MNS is the superior temporal sulcus. While not

considered a primary MNS region per se, the superior temporal sulcus is normally activated when visually observing a biological movements (Allison, Puce and McCarthy, 2000), transferring this visual information to the inferior parietal lobule for specific kinesthetic coding of the action. This information is then transferred to the IFG to define the goal of the action (Arbib et al. 2000, Iacoboni 2005; Iacoboni et al. 2001, Rizzolatti and Craighero 2004).

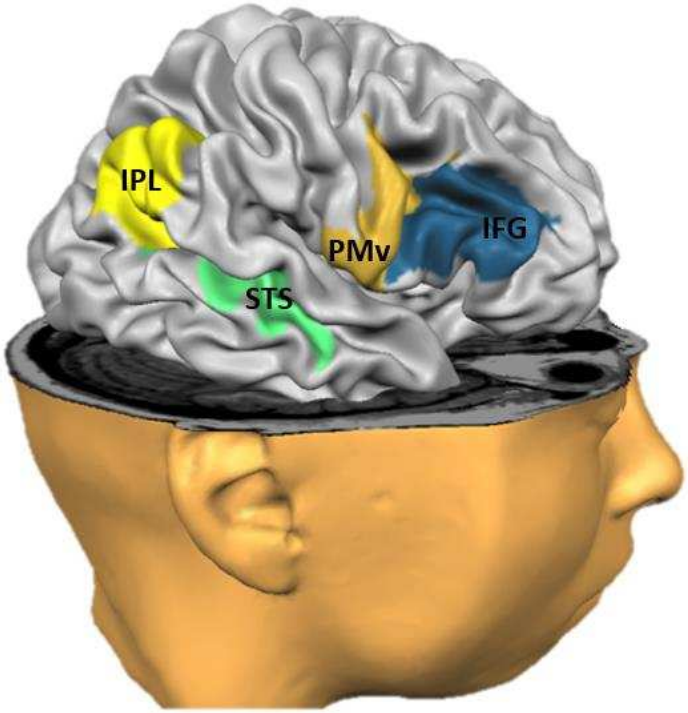

Fig. 1 Lateral view of cortical areas associated with the parieto-frontal mirror neuron system. IFG, inferior frontal gyrus (BA 44); PMv, ventral premotor cortex (BA 6); IPL, inferior parietal lobule; STS, superior temporal sulcus (created using BrainVoyager Brain Tutor: http://www.brainvoyager.com/products/braintutor.html; Goebel, Esposito, & Formisano, 2006).

The MNS has visual and motor properties (Fogassi and Gallese 2002) and is activated both when observing and executing a movement (Gallese et al. 1996, 2002; Aziz-Zadeh et al. 2006). It is not limited to hand and arm movements, but is also activated during observations of actions made by the mouth, foot, or whole body (Buccino et al. 2001, Calvo-Merino, 2005). One functional role of the MNS is action understanding, especially in the case of an incomplete visual stimulus (Umiltà et al. 2001). It is thought that this allows the individual to infer the end of the sequence or goal of the action by creating an internal representation of the

full action without seeing the entire action occurring (Umiltà et al. 2001). Lastly, the MNS is thought to play an integrative role in observational learning, forming a core circuit for action imitation, and enabling the learning and acquisition of new skills through modelling behavior and action of others (Billard and Arbib 2002).

Recently, several behavioral studies have examined the imitative ability of children with and without DCD; these studies have identified that children with DCD have difficulty imitating simple and complex gestures (Elbasan et al. 2012; Goyen et al. 2011), as well as meaningful actions (Dewey 1993; Sinani et al. 2011; Zoia et al. 2002). Although no neuroimaging studies have specifically studied imitation deficits in children with DCD, a recent fMRI study conducted by Licari et al. (2015) found that children with DCD had decreased activation in the left IFG, a region thought to have mirror properties (Iacoboni and Dapretto 2006; Iacoboni et al. 1999). As the task performed in the scanner involved participants imitating a finger sequencing task, the authors suggested that the decreased activation in the IFG may reflect a MNS dysfunction. Zwicker et al. (2010) also found similar differences where children with DCD recorded less activation in the left IFG, although no imitation was involved in this task. In addition to evidence from both behavioral and neuroimaging research, Werner and colleagues (2012) recently conducted a review, and Reynolds et al., (in press) a systematic review on the MNS and DCD. The authors gathered supportive evidence of activation differences in mirror neuron regions from DCD neuroimaging studies and hypothesized that a dysfunction in the MNS may underlie the imitation and movement impairments in DCD. However, the authors indicated a need for further neuroimaging studies to examine the neural correlates of DCD specifically under conditions that would enable the functioning of the MNS to be examined in greater detail. Hence, this study's primary aim is to determine if evidence of a MNS dysfunction exists in children with DCD with the use of functional neuroimaging techniques.

To date, no published fMRI studies have been conducted to directly examine imitation and MNS function in children with DCD. Therefore, the present study aimed to investigate whether a deficit in the MNS exists in children with DCD by examining cortical activations during the performance of an imitative finger sequencing task through the use of fMRI under three conditions: (i) action observation, (ii) action execution and (iii) action imitation (Aziz-Zadeh et al. 2006; Iacoboni et al. 1999; Licari et al. 2015). It was hypothesized that there will be decreased activation in the MNS of children with DCD, specifically in the pars opercularis of the IFG, ventral premotor cortex, inferior parietal

lobule, and superior temporal sulcus, most prominent during the action imitation condition. In addition, this study also explored other cortical areas that may contribute to the movement difficulties seen in children with DCD.

2. Methods

2.1 Participants

Twenty-seven right-handed male children, aged 8 to 12 years participated in this study. Participants were divided into two groups: Group 1 consisting of 15 males with DCD, one of whom was later excluded as a result of excessive head movement during scanning (n = 14, $\overline{x}$ = 10.08 years ± 1.31, range = 7.83 - 11.58 years), and Group 2 consisting of 12 group age-matched typically developing controls ($\overline{x}$ = 10.10 years ± 1.15, range = 8.33– 12.00 years). Only males were recruited to eliminate potential gender differences that may exist in cortical activation patterns (Cheng et al. 2006), or imitation ability (Chipman and Hampson 2007). Participants in Group 1 were recruited from the Paediatric Exercise Programs at The University of Western Australia (UWA). Children are referred by a range of clinicians to these programs based on their movement difficulties interfering with their daily living, which stem from a range of neurodevelopmental (including DCD), and other disorders, to undertake one-on-one, or group, movement-based intervention programs. The participants were currently attending these programs, with participation usually spanning multiple years. Although not all children had a formal diagnosis of DCD, inclusion was based on movement difficulties interfering with their daily living evidenced through referral to our programs, and MABC-2 scores $\leq 16^{th}$ percentile. Group 2 participants consisted of a convenience sample obtained from the community. All children from both groups attended regular schools. Ethics approval was obtained from the Human Research Ethics Committee (RA/4/1/5275) at UWA. Written consent was obtained from parents prior to the commencement of the study and ongoing verbal assent from participants throughout each phase of the study.

2.2 Experimental Design

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. Participants also completed a practice fMRI session to familiarize themselves with the scanning environment (noise, confined space, head coil and restraints), to practice the behavioral task to be performed, as well as develop skills to enable them to lie still for a readable scan. This familiarization protocol has been used successfully in previous investigations by researchers involved in this study (Licari et al. 2015). The second session involved the use of fMRI to examine differential brain activations as children performed a finger sequencing task. This session was conducted at the Department of Radiology at Sir Charles Gairdner Hospital.

2.3 Screening Assessments

Motor proficiency was assessed using the Movement Assessment Battery for Children – 2nd edition (MABC-2) (Henderson, Sugden et al. 2007). The total score for each task was adjusted for age, summed and converted into a percentile where a score of $\leq 16^{th}$ percentile indicated low motor proficiency and $\geq 20^{th}$ percentile indicated normal motor proficiency. Due to the comorbidity of DCD with other neurodevelopmental conditions such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), children with a diagnosis of these disorders were excluded to reduce potential confounding factors. In addition, the Swanson, Nolan and Pelham-IV (SNAP-IV) ADHD questionnaire (Bussing et al. 2008) and the Childhood Autism Rating Scale (CARS) (Saemundsen et al. 2003; Schopler et al. 1988) were used to assess symptoms of ADHD and autism, and children scoring within a clinical symptom range were also excluded. Handedness was screened using the Edinburgh Handedness Inventory (EHI; Oldfield 1971) and only right-handers (score ≥ 40) were included. Lastly, the Postural Praxis imitation test of the Sensory Integration and Praxis Tests (SIPT) developed by Ayres (1972) was used to assess participants' imitative ability. The test involved participants imitating a series of novel meaningless postures accurately and quickly (e.g. 'one hand on side of head, other hand on hip, head and trunk leaning'; Ayres, 1972). Results were computer generated by Western Psychological Services headquarters in California.

2.4 Behavioral Task

Participants performed a finger sequencing task (Licari et al. 2015) (see Fig. 2) using

their dominant (right) hand under three separate conditions: (i) action observation, (ii) action execution, and (iii) action imitation; a common protocol in previous MNS fMRI studies (Aziz-Zadeh et al. 2006; Iacoboni et al. 1999; Molenberghs et al. 2009). The finger sequencing task to be observed and executed remained the same across all conditions.

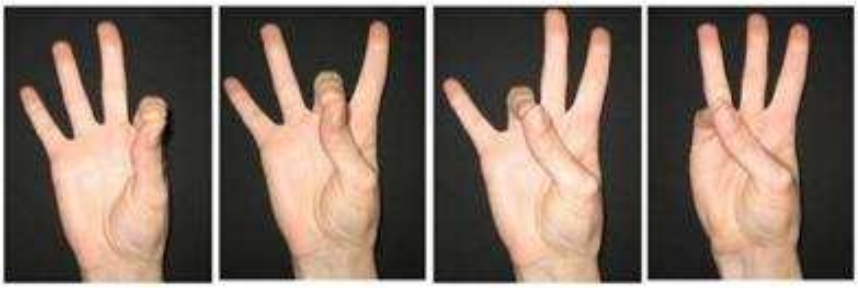

Fig. 2 Finger sequencing task. Right hand images were presented one at a time (for 1.2 seconds each) for the participants to follow in the action observation and imitation conditions.

During action observation, participants viewed the finger sequencing task and were prompted with a red colored circle to observe the sequence but not execute or imitate the task. In the action execution condition, participants were prompted by a green colored circle to perform the finger sequencing 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 colored circle to imitate the actions as they observed them. Each condition lasted for approximately 18 seconds with 12 seconds of rest (baseline condition) between each to allow for the blood-oxygen-level dependent (BOLD) response to return to baseline. Participants completed a total of eight repetitions of each condition performed in a randomized ordered across the two six-minute functional scans. Along with the visual cues, a metronome tick (0.8 Hz) was used to coordinate the timing of movements performed in each condition. An assessor observed the performance of tasks within the scanner to ensure tasks were completed correctly. While no quantitative measures were obtained, both groups appeared to successfully perform the finger sequencing task, and to perform the correct movements required for the conditions presented.

2.5 Imaging Parameters

Neuroimaging was conducted using a 3.0 Tesla Philips Magnetic Resonance Scanner,

with participants wearing an 8-channel head coil. High-resolution anatomical images were acquired first (254 s; T1-weighted 3D FFE 160 slices 0.575 mm× 0.575 mm × 1 mm), followed by two six minute functional studies. Total scan time was 18.5 min. The participants' heads were restrained with soft pads to prevent small, unwanted movements from causing artifacts. A strap was used also to help immobilize the wrist and forearm of the active hand during the scan in order to minimize participant head movement during scanning.

Functional images were collected using 25 slices covering the whole brain (slice thickness 4 mm, inter-slice distance 0mm, in-plane resolution 1.8mm×1.8mm) with an echo planar imaging sequence (TR = 3s, TE = 35ms, flip angle = 90°). 120 scans (plus 2 dummy scans) per run were acquired. This study employed a block design and all fMRI data analysis was carried out using SPM8 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. In-scanner motion was checked for each participant, one DCD participant was removed at this stage for displaying >9mm of motion. All other participants displayed minimal motion (<1.5mm) and there was no apparent difference between the DCD and control groups. This outcome advocates the benefits of having pre-scanning training sessions for children participating in experimental studies. A stringent fourth degree b-splice interpolation realignment procedure was applied to the images to realign to the first image in the sequence. Functional images were co-registered to the structural image. All 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.

Each run was split into blocks to reflect the observation, 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 128s (Friston et al. 2000). When estimating 1^{st} and 2^{nd} level contrasts, the effect of multiple comparisons in MRI data was corrected for by calculating the Family Wise Error (FWE) rate to remove activations that may have occurred by chance at any predetermined threshold (Worsley et al. 1992). An extent threshold of $k > 5$ voxels was set. In order to examine the signal activation patterns of the MNS, the present study contrasted the main effect of each individual condition (i.e. observation, execution and imitation) against rest/baseline using exploratory whole brain

analysis. Second level between-group contrasts were performed for each condition first performed at a FWE corrected level of $p < 0.05$, followed by an uncorrected level of $p < 0.001$ when no activation differences were identified at a corrected level. Second level positive and negative correlations with behavioral data at a whole brain level were first run at an uncorrected level of $p < 0.001$, followed with a cluster level significance set at $p < 0.05$.

Percent signal change values were extracted from 15 a priori regions of interest created in MarsBaR region of interest toolbox for SPM (MarsBaR: http://marsbar.sourceforge.net/). Each region of interest consisted of a 10mm diameter sphere, centered on the coordinates reported in the study by Aziz-Zadeh et al. (2006). This included regions in the pars opercularis of the IFG, supplementary and premotor areas, posterior parietal lobe, and superior temporal sulcus.

3. Results

3.1 Clinical Characteristics of Participants

The clinical data of participants are presented in Table 1. Group differences were observed in participants' motor proficiency, imitative ability and autistic traits. As expected, the DCD group had significantly poorer motor performance as compared to the control group on the MABC-2 ($p < 0.001$; Henderson et al. 2007). From the Postural Praxis assessment, children with DCD were found to have significantly decreased imitative performance as compared to the control group ($p < 0.05$). Interestingly, there was a significant difference in autistic symptoms between groups ($p < 0.01$) even though none of the children with DCD had a formal diagnosis of the disorder. No significant differences were found in the age and screening assessments for ADHD and handedness.

Table 1 Clinical Characteristics of Participants (DCD and Typically Developing peers)

	DCD (N=14)		TD (N=12)		t	p
	Mean	SD	Mean	SD		
Age (years)	10.08	1.31	10.1	1.15	0.380	0.970
MABC-2 (percentile)	6.89	9.59	49.5	23.7	5.982	<0.001
SNAP-IV ADHD	0.7	0.53	0.58	0.43	0.596	0.557
CARS	19.21	4.66	15.25	0.87	2.898	0.008

EHI	70.05	16.54	71.47	17.39	0.51	0.833
Postural Praxis	21.64	6.74	27.58	3.53	0.004	0.011

3.2 Whole Brain Analysis

The first stage in the analysis was to ensure that MNS regions were activated during the task paradigm. Based on MNS theory, and activation patterns among healthy controls of varying skill levels (Calvo-Merino et al. 2005), it was hypothesized that both children with and without DCD would display varying extents of MNS activation. As a result, the DCD and control group were collapsed and a series of whole brain analysis were carried out to identify if cortical areas typically associated with the MNS were activated during the tasks. To explore MNS activation patterns and identify whether there was a characteristic progressive increase in BOLD signal from action observation, to action execution and to imitation (Aziz-Zadeh et al. 2006; Iacoboni et al. 1999) during the sequencing task, the main effect of the observation condition was contrasted against baseline, and the execution and imitation conditions contrasted against observation. Importantly, activation in MNS regions was identified. During the observation condition, there were significant activation clusters in the extrastriate cortex of the occipital lobe (BA 18 and BA 19) compared to baseline (see Fig. 3). Furthermore, when children performed the task in the action execution (dark green in Fig. 3) and action imitation (light green in Fig. 3) conditions, compared to the observation condition, additional clusters of activation were reported in the postcentral gyrus, medial frontal gyrus and insula. A small cluster in the IFG had a higher activation during the execution than observation condition. Interestingly, there were no differences in cortical activation when the execution and imitation conditions were compared. All of the specific regions with coordinates where differences were seen across the conditions are presented in both Table 2 and Figure 3.

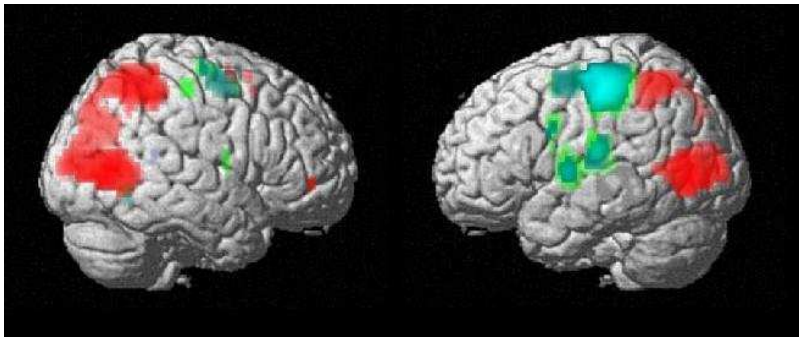

Fig. 3 Main effect of observation > baseline (red; FWE, $p < 0.05$), execution > observation (dark green; FWE, $p < 0.05$), and imitation > observation (light green; FWE, $p < 0.05$) for collapsed DCD and control groups (fading represents depth on image; all regions represented listed in table 2).

Table 2 Whole brain analysis for collapsed DCD and control groups – Condition comparison

Anatomical Region	Cluster (k)	Talairach Coordinates			Brodmann Area
		x	y	z	
Observation > Baseline					
Middle Occipital Gyrus (R)	2279	47	-72	5	19
		28	-87	10	19
Precuneus (R)		22	-55	56	7
Middle Occipital Gyrus (L)	804	-47	-72	5	19
		-31	-88	6	18
Cuneus (L)		-20	-91	6	17
Middle Frontal Gyrus (R)	9	33	2	57	6
	10	37	48	-4	10
Precuneus (L)	6	-22	-76	35	19
	417	-24	-52	52	7
Execution > Observation					
Postcentral Gyrus (L)	934	-38	-24	55	3
Medial Frontal Gyrus (L)	244	-4	-3	50	6
Insula (L)	382	-45	-4	6	13
		-40	-19	14	13
Postcentral Gyrus (L)		-51	-19	18	43
Culmen (R)	9	6	-57	-6	-
Postcentral Gyrus (R)	22	51	-21	51	2
	23	37	-10	58	6
	13	46	0	9	44
Inferior Frontal Gyrus (L)	22	-56	6	27	9
Thalamus (L)	52	-17	-24	10	Pulvinar
Imitation > Observation					
Postcentral Gyrus (L)	681	-38	-24	55	3
Medial Frontal Gyrus (L)	157	-4	-3	50	6
Insula (L)	89	-40	-19	14	13
Postcentral Gyrus (L)		-49	-19	18	43
Insula (L)	40	-45	-4	6	13

3.3 Whole Brain Analysis: Group X Condition Comparison

When group differences were compared individually within each condition, the

control group was found to have significantly more activation than the DCD group during observation compared to baseline in the right pars opercularis of the IFG, the precentral gyrus bilaterally, the left middle temporal gyrus, left posterior cingulate, and the right precuneus (Table 3 and Fig. 4). No significant differences were seen between groups in the action execution condition or action imitation conditions when run at uncorrected value of $p < 0.001$.

Table 3 Between group analysis of observation > baseline condition

Anatomical Region	Cluster (k)	Talairach Coordinates			Brodmann Area
		x	y	z	
Control > DCD					
Inferior Frontal Gyrus (R)	7	58	6	27	9
Precentral Gyrus (L)	44	-45	-8	35	6
(R)	30	54	1	39	6
Middle Temporal Gyrus (L)	12	-35	-56	12	19
		-36	-53	4	19
Precuneus (R)	9	14	-66	20	31
Posterior Cingulate (L)	40	-24	-61	9	30

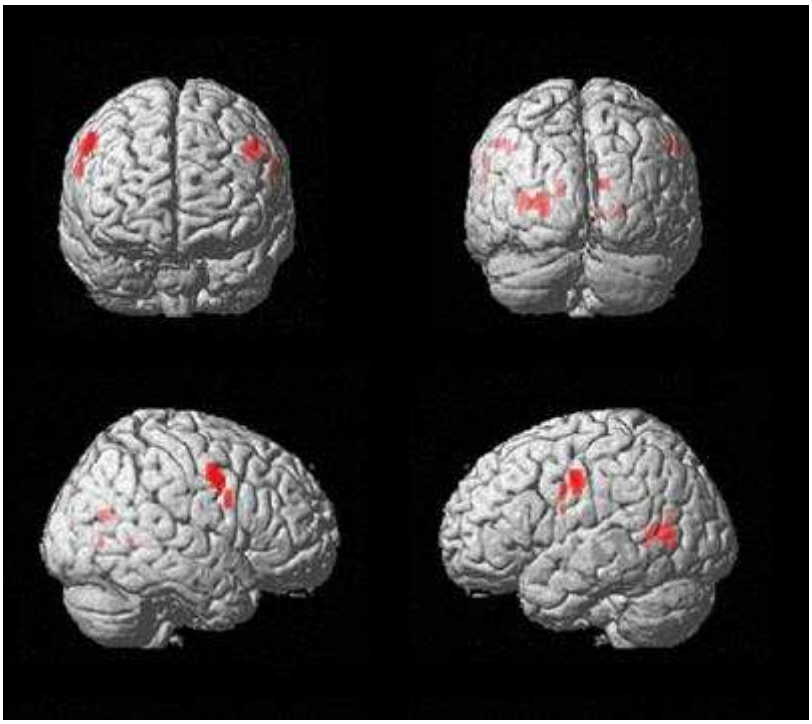

Fig. 4 Brain regions showing significantly greater activation for controls vs. DCD during observation condition > baseline ($p < 0.001$, uncorrected; fading represents depth on image; all regions represented listed in table 3).

3.4 Regions of Interest Analysis

A series of 2×3 mixed ANOVAs were run in MATLAB (http://mathworks.com/; code: Johnson, 2010) for each region of interest (Fig. 5) on the percent signal change values extracted from individual participants. Region of interest analysis yielded a significant ($p < 0.05$) a main effect for task condition in mirror neuron regions including the pars opercularis, posterior parietal regions (inferior parietal lobule), supplementary and premotor areas as well as the superior temporal sulcus (see Table 4). Post-Hoc analysis (Bonferroni corrected within each ROI, $p < 0.0083$) revealed significantly greater activations during both the execution and imitation conditions compared with observation condition in the posterior parietal regions, premotor and supplementary motor areas. There was also increased activation during the observation condition when compared to the imitation condition in a region of the premotor cortex (BA 6). No significant between-group differences were observed. An interaction effect between group and task condition was revealed in the pars opercularis (BA 44; x = -36, y = 14, z = 24), with the control group displaying greater activation during imitation compared to the DCD group; and vice versa for the observation condition ($p = 0.05$). Interestingly, compared to the control group (% signal change = 0.10, SE = 0.21), children with DCD (% signal change = -0.40, SE = 0.15) showed a large deactivation in the pars opercularis during the imitation condition (Figure 6).

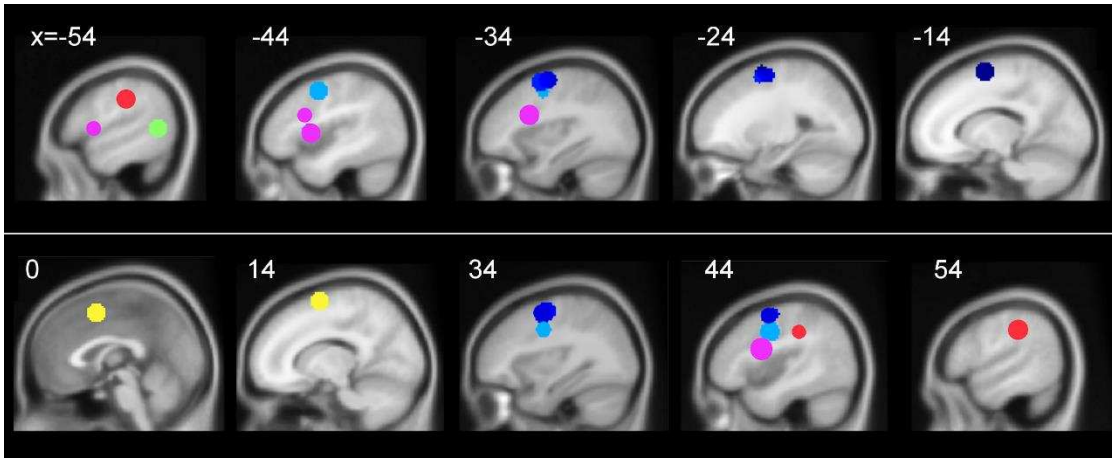

Fig. 5 Regions of Interest locations: Pars Opercularis (Magenta); Superior Temporal Sulcus (Green); Parietal (Red); Premotor Area (Blues); Supplementary Motor Area (Yellow).

Table 4 fMRI Region of Interest analysis of mirror neuron regions

Region of Interest												
Anatomical Region	Talairach Coordinates			Brodmann Area	F (between-subjects)	p	F (within-subjects)	p	F (interaction)	p	Bonferroni Post-Hoc ($p<0.0083$)	Difference between percent signal change of the beta values
	x	y	z									
Pars Opercularis	-47	8	6	44	0.204	0.656	3.915	**0.027**	1.613	0.210	Exe > Obs	0.177
	44	8	21	44	1.633	0.214	1.682	0.197	0.854	0.432	ns	ns
	-36	14	24	44	0.648	0.429	1.086	0.346	3.171	**0.050**	ns	ns
Superior Temporal Sulcus	-56	-58	6	21	0.672	0.420	4.379	**0.018**	0.614	0.545	Obs > Imi	0.144
Posterior Parietal/	-56	-26	36	40	2.103	0.160	5.201	**0.009**	0.322	0.727	Exe > Obs	0.184
Inferior Parietal Lobule	52	-30	38	40	2.01	0.169	1.494	0.235	0.074	0.929	ns	ns
Premotor Area	-32	2	58	6	0.233	0.634	2.944	0.062	0.172	0.842	ns	ns
	-42	0	48	6	1.281	0.269	2.062	0.138	1.043	0.360	ns	ns
	36	-4	56	6	0.467	0.501	10.028	**<0.001**	1.01	0.372	Exe > Obs	0.273
	38	-0.3	54	6	0.520	0.478	4.052	**0.024**	0.999	0.376	Exe > Obs	0.154
	41	-1	38	6	2.091	0.161	3.404	**0.041**	0.575	0.566	Obs > Imi	0.120
	-30	-5	60	6	0.825	0.373	28.407	**<0.001**	0.286	0.752	Imi > Obs	0.532
											Exe > Obs	0.603
	-16	0	64	6	1.339	0.259	4.052	**0.023**	0.188	0.829	Exe > Obs	0.154
Supplementary Motor	12	2	66	6	0.001	0.979	1.307	0.280	0.086	0.918	ns	ns
Area	1	6	52	6	1.389	0.25	1.387	**<0.001**	0.229	0.796	Exe > Obs	0.420
											Imi > Obs	0.371

Obs: Action Observation; Exe: Action Execution; Imi: Action Imitation
Negative x values reflect left hemisphere co-ordinates
Bold text ($p<0.05$)

3.5 Correlation with Postural Praxis imitation performance

Performance scores for imitation were entered as a covariate for the imitation > baseline contrast. Second level positive and negative correlations at a whole brain level were first run at an uncorrected level of $p < 0.001$, followed with cluster level significance set at $p < 0.05$. A positive correlation between imitation performance and activation clusters in the left caudate, claustrum, and anterior cingulate was observed (cluster level $p < 0.05$). An uncorrected negative correlation between activation in the right cingulate gyrus and posterior insula was also identified (uncorrected $p < 0.001$, $k > 75$).

Table 5: Imitation>Baseline activation correlated with imitation performance scores

Anatomical Region	Cluster (k)	Talairach Coordinates			Brodmann Area
		x	y	z	
Positive (uncorrected, p<0.001, cluster level p < 0.05)					
Caudate (L)	146	-8	12	16	Caudate Body
Claustrum (L)		-26	14	12	Claustrum
Anterior Cingulate (L)		-6	11	23	33
Negative (uncorrected, p<0.001, k > 75)					
Cingulate Gyrus (R)	88	22	-44	34	31
Posterior Insula (R)		31	-47	23	13

Given the established involvement of the pars opercularis in imitation (Caspers et al. 2010; Iacoboni et al. 1999), data were assessed for normality, following which Pearson correlations were run to explore the correlation between imitation performance on the Postural Praxis and activation values extracted from the three pars opercularis regions of interest during the imitation condition. Significant positive correlations were identified in two pars opercularis regions: TAL = -47, 8, 6, $r = 0.402$, $p = 0.042$; and TAL = -36, 14, 24, $r = 0.588$, $p = 0.002$.

4. Discussion

The present study examined cortical areas that may contribute to the movement difficulties seen in children with DCD, specifically suspected deficits in the functioning of the MNS regions. The DCD group was found to have reduced activation during the action observation condition in MNS related regions, including the precentral gyrus and IFG using

exploratory whole brain analysis. Using region of interest analysis, a significant interaction effect of group and task conditions in the pars opercularis (BA 44) was found, a key region of the MNS. Examination of the percentage signal change in this region of interest revealed a large deactivation of the pars opercularis in the DCD group during imitation of movement. The present study also found notable differences in regions outside the MNS including the middle temporal gyrus, and the posterior cingulate and precuneus (PCC/Pcu) complex during the action observation condition, with children with DCD displaying reduced activation compared to controls.

Of importance to the current study is the significant interaction effect of group and condition in the pars opercularis (BA 44), providing some preliminary support for MNS dysfunction in children with DCD. The pars opercularis of the IFG is a key component of the MNS and has been consistently observed to be critical for imitation (Heiser et al. 2003), involved in action observation (Rizzolatti et al. 1996a) and intention understanding (Fogassi et al. 2005). A further examination of the percentage BOLD signal change for the pars opercularis revealed that while there was a mean activation of this region in the control group, there was a large deactivation in the DCD group during the imitation condition. A deactivation in the BOLD signal has been reported to either reflect a local reduction in regional cerebral blood flow (rCBF) to less active brain regions or an inhibition of neural processes in brain regions that are not task relevant (Tomasi et al. 2006). It is unlikely that the deactivation of BOLD signal observed in the DCD group was a result of neural inhibition of task-irrelevant brain regions since the control group activated the pars opercularis during imitation, and numerous MNS studies have reported its involvement during imitation. Thus, the deactivation observed in the pars opercularis during imitation is likely to be the result of reduction in rCBF, and potentially reflects dysfunction in this area and differences in neural activation patterns of children with DCD. Interestingly, there was a moderate activation of the pars opercularis in the DCD group during the action observation condition. Furthermore, positive correlations between activation in the pars opercularis and behavioral imitation performance provides further evidence to suggest this region may be associated with the imitation impairments in DCD. These results raise the possibility that children with DCD may have used different strategies to complete motor tasks. In support of results from previous neuroimaging studies in this population (Zwicker et al. 2010, 2011), these activation patterns highlight the differential brain activation and recruitment patterns of children with and without DCD during performance of tasks.

Consistent with other MNS research (Buccino et al. 2001, 2004; Hari et al. 1998; Iacoboni et al. 1999; Rizzolatti et al. 1996a, 1996b), this study found activation of the precentral gyrus and IFG during the action observation condition. The precentral gyrus is also part of the primary motor area (M1) that plays a role in voluntary hand movements (Rose et al. 2012; Sanes et al. 1995) and motor imagery (Porro et al. 1996; Roth et al. 1996). The degree of activation within these regions, however, was not consistent between groups; a reduced level of activation in these areas in children with DCD compared to controls provides further support for potential dysfunction of the MNS and motor regions in this population. Activation of the precentral gyrus and IFG has consistently been observed during action observation and imitation studies (Caspers et al. 2010). Frontal MNS regions are thought to be involved in the coding of the goals of actions and the motor representation of observed movements (Iacoboni 2005; Iacoboni and Mazziotta 2007; Rizzolatti and Craighero 2004). Furthermore, the essential role of the IFG in the MNS circuitry is highlighted by the impaired imitation performance that results when the activation of this region is disrupted by rTMS (Heiser et al. 2003). Possible dysfunction, and differences in activation patterns of mirror neuron regions in children with DCD have important implications in terms of visual learning and movement acquisition strategies, possibly impacting the way children with DCD observe, plan, and execute actions.

Differential activation patterns observed in non-mirror regions also point to children with DCD experiencing difficulties with action observation and imitation. Despite not being a 'mirror' region, the middle temporal gyrus has been shown to activate during the observation of hand movements (Decety et al. 1997; Rizzolatti et al. 1996b), and interestingly, lesions centered on this region have been associated with disturbed imitation of hand postures (Goldenberg and Karnath 2006). The posterior cingulate and precuneus (PCC/Pcu) complex is a main area of the default-mode network, which activates during action observation and movement readiness (Astafiev et al. 2003; Treserras et al. 2009). In line with the reduced activation levels displayed in the DCD group during the observation condition, a study of action observation in expert and novice dancers (Calvo-Merino et al. 2005), found the activation of the posterior cingulate to be influenced by expertise with higher levels of activation in the expert group.

Activation in a number of non-mirror regions were identified to be positively correlated with imitation performance outside of the scanner environment. These regions, including the anterior cingulate, claustrum and the caudate, are involved in attentional

processes, prioritizing attention, and attention-demanding tasks (Berger and Posner 2000; Davis et al. 2000; Goll, Atlan and Citri 2015; Mathur 2014). The positive correlation between these regions and imitation performance possibly indicates that individuals who were more proficient at imitating postures outside the scanner, used greater attentional resources while imitating the finger sequencing during scanning. In line with this, a negative correlation between imitation performance outside the scanner and the cingulate gyrus (BA31) and posterior insula, functionally connected regions (Taylor, Seminowicz and Davis 2009), was identified. The posterior portion of the cingulate gyrus, is a component of the default mode network (Di and Biswal 2014; Shulman et al. 1997), the activation of which is anti-correlated with task performance (Rosazza and Minati 2011; Shulman et al. 1997; Uddin et al., 2009); this also suggests greater in-scanner task engagement for those who performed better on the behavioral task. Potential differences in attentional capabilities is consistent with research by Querne et al. (2008), which identified differences in attentional network connectivity strength in children with DCD compared to controls.

In addition to the group differences during observation and the group x condition interaction observed in the pars opercularis, there were some interesting within-subject patterns of activity seen within MNS regions in general. Complementing the whole brain activation maps, activation differences in mirror neuron regions were best seen between conditions using the region of interest analysis, with significantly greater activation during the execution and imitation conditions compared with observation in the posterior parietal regions, premotor and supplementary motor areas. These findings are consistent with those of Aziz-Zadeh et al. (2006) who found significant within-subject differences with activation greater during execution and imitation than the observation in the pars opercularis, inferior parietal lobule, premotor and supplementary motor areas (BA 6) as well as the superior temporal sulcus.

Unlike previous MNS research, however, where mirror neuron regions were found to follow an increasing pattern of signal activity (active during action observation, slightly more active for action execution and highest during action imitation) (Aziz-Zadeh et al. 2006; Iacoboni 1999), the present study did not find any significant activation differences between the execution and imitation conditions in the whole-brain or ROI analysis despite the imitation condition stimulus having a greater visual component. Furthermore, no group differences were observed for either the execution or imitation contrasts at a whole brain 2nd level analysis level, and no significant between group differences were identified for region

of interest percentage signal change values. These findings may in part be due to a learning effect from extensive practice of the finger sequencing task prior to scanning. Although both groups appeared to be successfully performing the sequencing task for both of these conditions, a limitation of the research is that no quantitative performance measures were collected. In addition, although participants in this study were instructed to use the visual prompts during the imitation condition, given the previous practice of the task, there is a possibility that they might have performed the sequencing movement in much the same manner as they did in the execution condition, performing the task from memory and relying on proprioceptive feedback. There were consistencies in the activation profiles of the postcentral gyrus, medial frontal gyrus and insula in both the execution and imitation conditions, providing further evidence of similarities between the two tasks. These areas are suggested to play important roles in motor control (Cunnington et al. 2002), motor learning (Mutschler et al. 2007), and also error processing (Mars et al. 2005; Ullsperger and Von Cramon 2004). To circumvent the possible effect of motor learning, further research into MNS function in this population would benefit from the use of simple finger movements based on previous MNS research (such as directing the finger towards a target) (Aziz-Zadeh et al. 2006) that have not been practiced extensively prior to scanning, as this might elicit a true imitation response.

In addition to the potential learning effect seen in the task, there are some other minor limitations in our work. Due to a lack of anatomical maps in children and similar functional data, the region of interest analysis was based on adult data (Aziz-Zadeh et al. 2006). Adults may not map on to children perfectly, but it was felt that basing the ROIs on established coordinates was more accurate and objective than using anatomical ROIs. In addition, differences were seen between groups on the CARS, with children in the DCD group displaying more autistic-like symptoms. Whilst MNS dysfunction and imitation deficits have been implicated in autism (Williams et al. 2006, Dapretto et al. 2006), some of the items within autism questionnaires typically include questions related to movement. For example, the CARS includes questions about whether the child can imitate sounds, words, and movements which are appropriate for his or her skill level and the child moves with the same ease, agility, and coordination of a normal child of the same age (Schopler et al. 1988). This may explain the slightly elevated scores seen within the DCD group on this questionnaire. Despite being statistically significant, the differences on these scales are likely not clinically significant with no children included who had scored within a clinical symptom range on

either questionnaire. One further limitation of the research is that not all children in the DCD group had a formal diagnosis of DCD, and inclusion was instead based on MABC-2 scores. Despite this, all participants in the DCD group were recruited through the Paediatric Exercise Programs at the University of Western Australia, with their program attendance a result of the impact of their low motor skill proficiency on their daily living. Finally, although the sample size is comparable with other studies in this population, the sample is small. As a result, uncorrected statistics have been reported for group comparisons, which may have overstated some of the results for the observation over baseline contrast relating to the hypothesized MNS regions.

5. Conclusion and Future Directions

This study is the first in providing a preliminary understanding of the MNS functioning in children with DCD and adds to the small number of imaging studies in this population. While the results should be interpreted with caution due to small sample size and uncorrected whole brain fMRI statistics, this study provides some evidence to suggest that MNS dysfunction may exist in children with DCD, and that they may have adopted a different neural strategy while observing, executing and imitating during the performance of the task. In addition to the different activation patterns within MNS regions, the current study also identified differences in brain activation patterns during the tasks in a number of regions outside of the MNS, which contribute to movement performance. Recent neuroimaging work has shifted from exploring isolated brain regions, towards exploring functional connectivity and interactions of neural areas (Rosazza and Minati 2011); future work to explore functional connectivity of MNS regions, and interactions between the MNS and other neural systems would also be of benefit in this population. Further research should investigate whether a MNS dysfunction in DCD may be localized to a particular phase of movement. This would provide better insights for professionals working with this population as they develop novel intervention strategies to address the associated motor impairments. For example, a number of motor skill intervention approaches based on MNS theory have been successfully used in other populations, such as action observation treatment (Ertelt et al., 2007) and motor imagery training (Buccino et al., 2006). Further research into MNS function has the potential to inform how these paradigms could be modified for use, and applied in a DCD cohort. Taken together, the mirror neuron hypothesis in DCD has potential in providing insights into

the associated neural mechanisms of the movement difficulties associated with this condition.

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Conflict of interest The authors declare they have no conflict of interest.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the Human Research Ethics Committees at the University of Western Australia (RA/4/1/5275) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all parents/guardians and ongoing verbal assent from individual participants included in the study.

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