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

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14
15 **Abstract**

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

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

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

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

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

37 **What this paper adds**

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

52

53 **Keywords**

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

56

57 **Highlights**

58 Children with DCD had reduced imitation and motor imagery performance

59 Children with and without DCD activated MNS regions

60 No group differences in MNS activation were identified

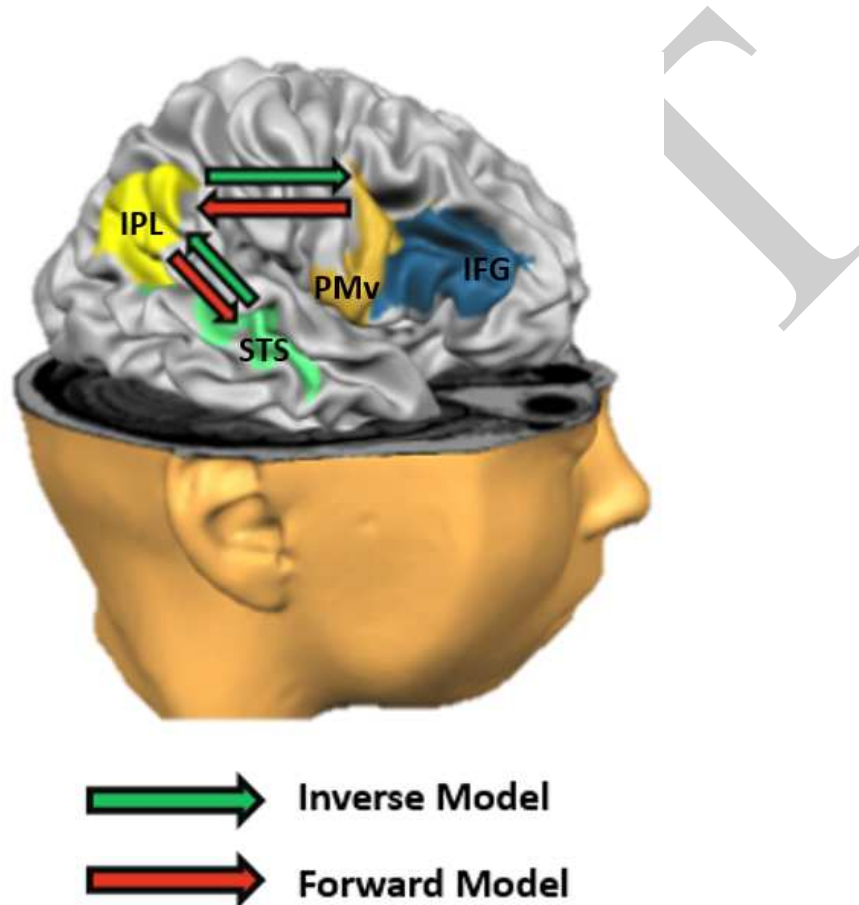
61 Small group differences were found in motor planning and attention brain regions

62 **1. Introduction**

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

80
81 The MNS circuit in humans is believed to incorporate the pars opercularis (BA44) of the inferior
82 frontal gyrus (IFG; Kilner, Friston, & Frith, 2007), the adjacent ventral premotor cortex (PMv;
83 BA6; Buccino et al., 2001; Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Rizzolatti et al., 1996) and
84 the rostral inferior parietal lobule (IPL; BA 39 and 40; Arbib, Billard, Iacoboni, & Oztup, 2000;
85 Caspers, Zilles, Laird, & Eickhoff, 2010; Rizzolatti & Craighero, 2004; Figure 1). These mirror
86 regions fire when one actively observes, imagines, executes, or imitates a movement, with a
87 progressive increase in functional MRI (fMRI) blood-oxygen-level dependent (BOLD) signal
88 from observation through to imitation (Aziz-Zadeh, Koski, Zaidel, Mazziotta, & Iacoboni, 2006).
89 Another important area involved in the MNS is the superior temporal sulcus (STS). Although STS
90 neurons are not activated during motor execution (Aziz-Zadeh, Koski, et al., 2006; Buccino,
91 Solodkin, & Small, 2006), this area is thought to be connected with mirror regions via the arcuate
92 fasciculus and parallel tracts (Catani, Jones, & ffytche, 2005; Iacoboni et al., 1999; Rizzolatti,

93 Fogassi, & Gallese, 2001) and is believed to play an important role in visual input during
94 observation by coding for goal-directed and meaningful actions (Jellema, Baker, Wicker, &
95 Perrett, 2000; Perrett et al., 1989). The human MNS has been proposed to represent a ‘dynamic
96 feedback control system’ (Schippers & Keysers, 2011, p. 40) that supports both forward and
97 inverse internal modelling processes, with a primary predictive control function (Figure 1).
98



99

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

104

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

109 2002). The use of motor imagery, on its own, and in conjunction with traditional motor execution
110 training, has repeatedly been shown to improve motor skill performance (Buccino et al., 2006) and
111 assist motor skill development and acquisition (Decety, 1996). Imitation of learned, meaningful
112 skills (Dewey, 1993; Sinani et al., 2011; Zoia et al., 2002) and non-meaningful simple and complex
113 gestures (Elbasan et al., 2012; Goyen, Lui, & Hummell, 2011; Reynolds et al., 2016) have been
114 shown to be performed poorly by children with DCD, who make more errors and respond slower
115 to visual cues. In addition to imitation deficits, children with DCD have difficulty with motor
116 imagery. Results on mental rotation and other motor imagery tasks suggest that children with DCD
117 are able to adopt the use of a motor imagery strategy; however, they make slower, less accurate
118 responses to stimuli (Adams et al., 2014, 2017; Fuelscher et al., 2016; Reynolds, Thornton, et al.,
119 2015).

120

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

140 adopting different neural strategies while performing the different task conditions, the lack of
141 expected MNS signal increase from execution to imitation at a whole brain level was interpreted
142 as a potential learning effect, whereby the extent of activation of MNS regions was likely reduced,
143 which may have prevented group differences during execution and imitation from being identified.
144

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

159 **2. Methods**

160 *2.1 Participants*

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

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

181

182 *2.2 Experimental design and screening assessments*

183 Participants were required to attend two testing sessions. During the first session, participants
184 completed motor and diagnostic screening assessments to ensure that they met the diagnostic
185 criteria for inclusion. Motor proficiency was assessed using the MABC-2 (Henderson, Sugden, &
186 Barnett, 2007). Due to the high level of comorbidity of DCD with other neurodevelopmental
187 disorders (Dapretto et al., 2006), children with a diagnosis of either autism spectrum disorder
188 (ASD), or attention deficit hyperactivity disorder (ADHD), or any neurological conditions
189 (Criterion D) were excluded from the study. In addition, the Childhood Autism Rating Scale
190 (CARS; Saemundsen, Magnusson, Smari, & Sigurdardottir, 2003; Schopler, Reichler, & Renner,
191 1988) and the Swanson, Nolan and Pelham-IV (SNAP-IV) ADHD questionnaire (Bussing et al.,
192 2008) were used to assess symptoms of ASD and ADHD. Handedness was screened using a child
193 modified version of the Edinburgh Handedness Inventory (Oldfield, 1971), and only right-handers
194 (score ≥ 40) were included to eliminate any potential brain lateralisation differences related to
195 handedness.

196

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

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

220

221 *2.3 Imaging parameters*

222 Imaging was conducted using a Philips Ingenia 3T Multi Transmit Wide Bore Scanner, with
223 participants wearing a 12-channel head coil. The participants' head was restrained with soft pads
224 to prevent small, unwanted movements from causing artefacts. A strap was used to help
225 immobilize both wrists and forearms to limit the movement of the active hand in order to minimize
226 participant head movement during scanning. A thermo-plastic splint was worn by participants on
227 the active dominant hand during scanning to isolate movement in the digits. High-resolution
228 anatomical images were acquired first (T1-weighted 3D FFE 175 slices $1 \times 1 \times 1$ mm), followed
229 by two eight minute functional studies (T2-weighted gradient echo, TR/TE = 3000/35 ms, flip
230 angle 90°, 25 axial slices with a thickness of 4 mm, interslice gap = 0 mm, in-plane resolution
231 1.8mm×1.8 mm). Total scan time was 22.5 min.

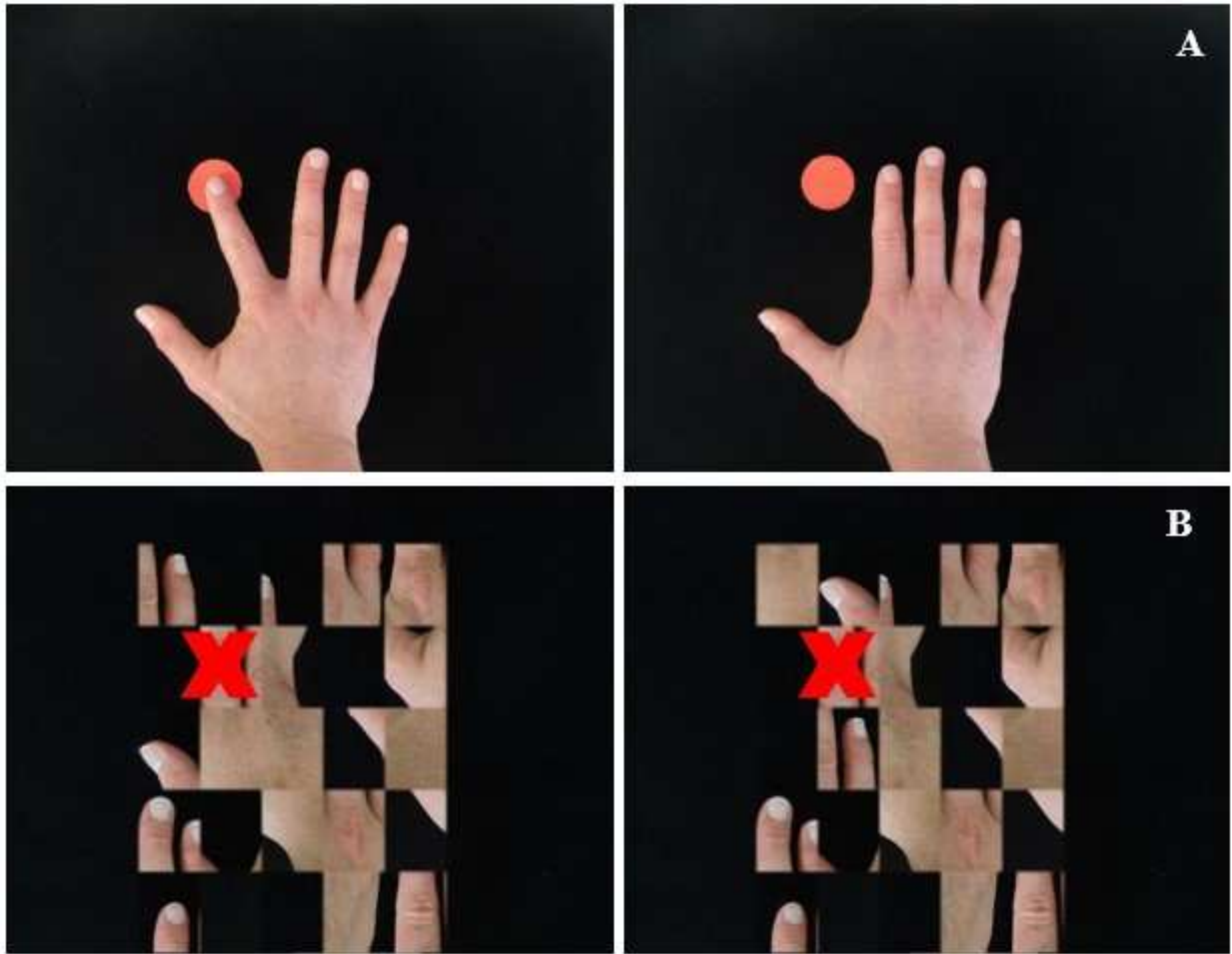
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233 *2.4 Scanning task*

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

249
250 Participants completed a total of eight repetitions of each condition in a randomized order across
251 two functional block design scans (four presentations per scan). Each condition lasted for
252 approximately 18 seconds with 12 seconds of rest (rest condition) between each to allow for the
253 BOLD response to return to baseline. The rest condition was a non-mirror neuron observation task
254 to isolate changes in brain responses to those evoked by the task; participants viewed two
255 scrambled hand images with a red cross, which were designed to have a similar contrast and
256 luminance in the center of the screen to the active condition images (modified version of: Aziz-
257 Zadeh, Iacoboni, & Zaidel, 2006). A smoothing function was applied to the edges of the scrambled
258 blocks to remove the sharp edges. Rest images also changed at a frequency of 1Hz along with a
259 metronome tick. An assessor in the scan room observed the performance of tasks within the
260 scanner to ensure tasks were completed correctly, however, no quantitative measures were
261 recorded. In addition, participants were asked whether they were imagining performing the task
262 for the imagery condition.

263



264
 265 **Figure 2.** A: Adduction/abduction finger tapping task condition images (observation example), B:
 266 Rest condition images.

267
 268 *2.5 Imaging analysis: Functional*

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

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

285
286 Each run was split into blocks to reflect the observation, motor imagery, execution, and imitation
287 task conditions outlined above. Individual statistical contrasts were set up by using the general
288 linear model to fit each voxel with a combination of functions derived by convolving the standard
289 hemodynamic response with the time series of the events and removing low-frequency noise with
290 a high-pass filter with a frequency cut off of 128 s (Friston et al., 2000). The six nuisance regressors
291 capturing head motion from each session that were created for each participant during the
292 realignment stage were built into the first level models as covariates. In order to examine the signal
293 activation patterns of the MNS, the main effect of each individual condition (e.g., observation,
294 motor imagery, execution, and imitation) was contrasted against the rest condition (to identify
295 brain regions activated by each task condition) using exploratory whole brain analysis. Contrasts
296 were run at a cluster corrected level, with voxel height thresholds set at $p < 0.001$ (uncorrected),
297 with an additional extent threshold set for each contrast to correct for multiple comparisons, thus
298 activations passed a cluster-level extent threshold of $p < 0.05$ (FWE corrected; Friston, Holmes,
299 Poline, Price, & Frith, 1996; Nichols & Wilke, 2012). Second level between-group contrasts
300 (control > DCD; DCD > control) were performed for each condition, first at a cluster corrected
301 level of $p_{\text{FWE}} < 0.05$. Where no activation differences were identified at a corrected level, contrasts
302 were re-run at an uncorrected level of $p < 0.001$. All significant clusters extracted in MNI
303 coordinates were converted to Talairach coordinates; the nearest grey matter structure, and
304 Brodmann area were identified using Talairach Client (<http://www.talairach.org/>; Lancaster et al.,
305 1997; Lancaster et al., 2000) and the Co-Planar Stereotaxic Atlas of the Human Brain (Talairach
306 & Tournoux, 1988).

307

308 Region of interest (ROI) analysis was also conducted in pre-selected locations to explore signal
309 patterns in MNS regions. Percent signal change values were extracted from 15 ROIs created in
310 MarsBaR region of interest toolbox for SPM (MarsBaR: <http://marsbar.sourceforge.net/>; Brett,
311 Anton, Valabregue, & Poline, 2002) in SPM8. Following Reynolds and colleagues (Reynolds,
312 Licari, Billington, et al., 2015), each ROI consisted of a 10mm diameter sphere, centered on the
313 coordinates reported in the study by Aziz-Zadeh et al. (Aziz-Zadeh, Koski, et al., 2006). This
314 included mirror regions in the pars opercularis of the IFG (BA44: $x=-47$ $y=8$, $z=6$; $x=44$, $y=8$,
315 $z=21$; $x=-36$, $y=14$, $z=24$), supplementary (BA6: $x=12$, $y=2$, $z=66$; $x=1$, $y=6$, $z=52$) and premotor
316 areas (BA6: $x=-32$, $y=2$, $z=58$; $x=-42$, $y=0$, $z=48$; $x=36$, $y=-4$, $z=56$; $x=38$, $y=0.3$, $z=54$; $x=41$, $y=-$
317 1 , $z=38$; $x=-30$; $y=-5$; $z=60$; $x=-16$; $y=0$; $z=64$), inferior /posterior parietal lobe (BA40: $x=-56$, $y=-$
318 26 , $z=36$; $x=52$, $y=-30$, $z=38$), and STS (BA21: $x=-56$, $y=-58$, $z=6$). A series of 2×4 mixed
319 ANOVAs were run for each ROI on the percent signal change values extracted from individual
320 participants. As a result of the lack of anatomical maps in children and similar functional data, the
321 ROI analysis was based on established coordinates from adult MNS data (Aziz-Zadeh, Koski, et
322 al., 2006). Although adults do not map on to children perfectly, it was felt that this approach was
323 more accurate and objective than the use of anatomical ROIs.

324

325 **3. Results**

326 The final sample consisted of 19 participants (10 DCD; nine controls). The characteristics of this
327 group are presented in Table 1. Groups were well matched for age, with no significant difference
328 identified between the DCD (8.25 – 12.75 years) and control groups (8.33 – 12.25 years). By
329 inclusion criteria of the groups, children with DCD had significantly poorer motor proficiency
330 compared to the controls on the MABC-2 ($p < 0.001$), with the DCD group ranging from the 1st –
331 16th percentiles, and controls from the 37th – 98th percentiles. Consistent with previous research
332 (Reynolds, Licari, Billington, et al., 2015), children with DCD displayed significantly more
333 ADHD and autistic symptoms ($p < 0.05$), however, none of the children with DCD had a formal
334 diagnosis of either disorder. Both questionnaires include questions about engagement in movement
335 related activities, which is likely, in part, to explain these group differences. Children with DCD
336 were found to have significantly decreased imitative ability as compared to the control group on
337 both the postural and sequencing praxis, and reduced accuracy levels for the motor imagery task
338 ($p < 0.05$).

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

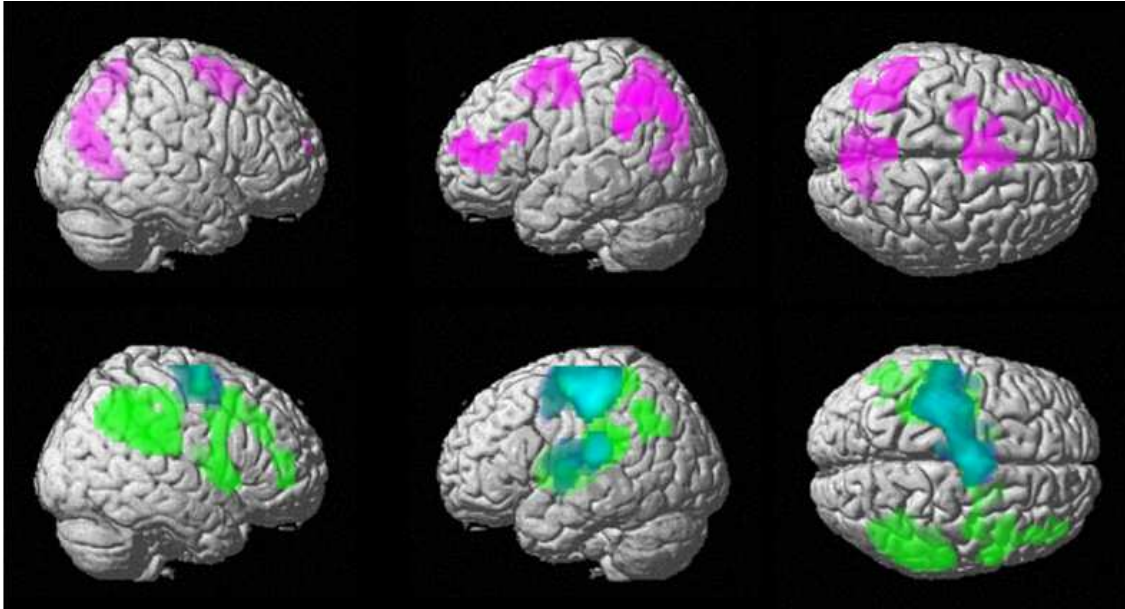
	DCD (N=10)		TD (N=9)		t/U	p	d
	Mean/ Median	SD/ IQR	Mean/ Median	SD/ IQR			
Age (years) ^a	10.18	1.34	10.41	1.17	0.401	0.694	0.18
MABC-2 (percentile)	7.80	5.40	70.11	23.04	7.922	<0.001**	3.72
CARS ^a	17.90	2.18	15.22	0.36	2.964	0.009*	1.57
SNAP-IV ^a	0.87	0.53	0.31	0.22	3.820	0.004*	1.33
Postural Praxis ^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*	-

340

341 *3.1 fMRI whole brain analysis: Condition contrasts*

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

358



359

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

363

364 3.2 fMRI whole brain analysis: Group contrasts

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

371

372 Group comparisons were also run for the imitation > execution, imitation > motor imagery, and
 373 imitation > observation contrasts, to explore regions that were more active when participants had
 374 to attend to and move in time with the visual stimuli, as opposed to just executing the movement
 375 without prompting visual stimuli, imagining without moving visual stimuli, or just watching the
 376 stimuli respectively. A number of uncorrected ($p < 0.001$) small clusters were identified in all three
 377 control > DCD contrasts (Table 4). There were no significant clusters for any of the DCD > control
 378 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

381 **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

382

383 **Table 4.** Between group analysis of imitation > observation, imagery, and execution conditions
384 (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

385

386 3.3 *fMRI region of interest*

387 Using ROI percentage signal change analysis, significant main effects for task condition were
388 observed in mirror neuron regions with a trend for increasing signal activations across the
389 conditions to imitation. Post-Hoc analyses revealed significant within-subject differences with
390 greater activation during the motor imagery, execution and imitation conditions compared with the
391 observation condition in the posterior parietal regions, premotor and supplementary motor areas,
392 and greater activation for motor imagery compared to observation in the pars opercularis. A
393 significant group difference was identified in the right posterior parietal/inferior parietal lobe ($x =$
394 $52, y = -30, z = 38, BA40, F = 4.570; p = 0.047$), with controls having increased activation across
395 conditions, compared to the DCD group (mean difference = 0.085). No significant condition x
396 group interactions were found.

397

398 4. Discussion

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

417

418 The design of this study was based on previous MNS research (Reynolds, Licari, Billington, et al.,
419 2015), incorporating additional MNS activation states using a novel task without prior practice to
420 examine MNS function. The activation profiles observed at a within-subject level revealed that
421 both groups effectively activated MNS regions, including the inferior and medial frontal gyri, and
422 inferior parietal lobule, as well as other expected motor regions. Furthermore, an examination of
423 the percentage signal changes in the ROI analyses revealed the expected increase in signal
424 activation trends across conditions. Although there were no significant activation clusters for the
425 observation > rest contrast, which we would expect to see (Caspers et al., 2010), it is possible that
426 the rest condition, which also incorporated moving images, activated some mirror regions. Despite
427 this, based on the consistent MNS activation patterns observed during the other task conditions,
428 and across the conditions at a ROI level, any group differences at a neurological level in this system
429 impacting movement execution would still be expected to be identified. Furthermore, an
430 examination of the percentage signal changes in the ROI analysis revealed the expected increased
431 signal activation trends across conditions from observation to imitation (Aziz-Zadeh, Koski, et al.,
432 2006), suggestive of mirror region activation during the tasks. The increasing activation at whole
433 brain and ROI levels across the conditions suggests that a practice effect was not encountered as
434 it may have been in previous research (Reynolds, Licari, Billington, et al., 2015). The similar
435 activation patterns observed by both the DCD and control groups across most ROIs, suggests that
436 both groups activated mirror neuron regions to perform the tasks, with no differences in MNS
437 activation patterns to support a deficit in this system at a neurological level.

438

439 The absence of between-group differences in MNS activation at a whole brain level is consistent
440 with the results from the previous fMRI research by our research group (Reynolds, Licari,
441 Billington, et al., 2015). Given the evidence for MNS dysfunction in DCD at a behavioural level
442 in conjunction with differences in MNS activation patterns during other functional tasks
443 (Debrabant et al., 2013; Kashiwagi et al., 2009; Licari et al., 2015; Querne et al., 2008; Reynolds,
444 Licari, Billington, et al., 2015; Zwicker et al., 2010, 2011), the minimal group differences in MNS
445 activation had previously been hypothesized to be the result of a learning effect. Recent fMRI
446 research by Kashuk and colleagues (2017) identified a number of small clusters of decreased
447 activation 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 difficult 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 &

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

492
493 Deficits in motor planning, generating internal models and the use of feedforward information
494 have previously been hypothesized to underlie the movement difficulties characteristic of DCD
495 (Adams et al., 2014). The small reduced activation clusters in planning and attention regions during
496 imitation in children with DCD provide preliminary support for dysfunction of motor planning and
497 attentional processes neurologically. Differential activation and connectivity patterns in motor
498 planning and attention regions have also been identified in children with DCD in other fMRI and
499 rsfMRI studies (Debrabant et al., 2013; McLeod et al., 2014; Querne et al., 2008; Zwicker et al.,
500 2010). In addition, reduced grey matter volumes in motor planning and attention regions have been
501 reported (Reynolds et al., 2017). Interestingly, research on other neurodevelopmental disorders
502 with movement difficulties, such as ADHD, also implicates these neural regions and processes
503 (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Schrimsher, et al., 2002). In conjunction with
504 the high levels of comorbidity associated with DCD, the incorporation of combined comorbidity
505 groups in neuroimaging research may be beneficial for future research.

506
507 While this study found no evidence to support the MNS theory of motor impairment, there are
508 some limitations to our work to consider. Although the adduction/abduction finger tapping task
509 has been shown to activate MNS regions in previous research, the task itself is relatively simple

510 due to task constraints within a scanning environment. Imagery of simple tasks has, however, been
511 shown to activate cortical networks comparable to those activated during complex imagined tasks
512 (Szameitat, Shen, & Sterr, 2007). Despite this, it is possible that group differences may have
513 become more apparent with a more complex task (Kuhtz-Buschbeck et al., 2003); however,
514 performing a complex unlearned task during scanning is likely to present a challenge for children
515 with DCD, as well as those without. As the sample size is small, although comparable with other
516 studies in this population, uncorrected statistics have been reported for group comparisons and
517 should be interpreted with caution. Given the small sample size, the study may have been under-
518 powered to detect MNS differences between groups. To keep scan time to a minimum, the volume
519 was reduced and did not extend down to the cerebellum. This brain region has been implicated in
520 DCD (Marien, Wackenier, De Surgeloose, De Deyn, & Verhoeven, 2010; Zwicker et al., 2010,
521 2011), however, as this study was specifically exploring MNS, a trade-off was made to instead
522 increase the number of task presentations in the fMRI protocol.

523

524 **5. Conclusions and future directions**

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

540

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