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Neuroimaging Findings for Developmental Coordination Disorder (DCD) in Adults: Critical Evaluation and Future Directions

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Abstract

Approximately 75% of those diagnosed with developmental coordination disorder (DCD) exhibit motor problems in adulthood. Neuroimaging studies promise to reveal the endophenotypes of mature brain systems affected by DCD. The aim here was to review these publications. Bibliographic searches identified papers published before June 2019. Neuroimaging results revealed: functional abnormalities in the prefrontal, frontal and occipital regions, superior parietal lobe and cerebellum; structural white matter abnormalities in the corticospinal tract, internal capsule and inferior and superior longitudinal fasciculi; significantly reduced interhemispheric cortical inhibition within the primary motor cortex (hPMC); lack of increased hPMC activity during a motor imagery task and a reduced leftwards brain asymmetry for speech. These results suggest complex endophenotypes for adults with DCD (DCDAs). However, the studies have shortcomings. For instance, all relied upon small and unrepresentative samples. Gender and age were not tested systematically. The effects of many co-occurring disorders were not controlled. Most studies relied on between group comparisons, which, given the heterogeneity of DCD, may obscure the results for underrepresented cases. Overall, the young field of neuroimaging studies of DCDAs reported interesting results; however, there is an urgent need for investigations to address these shortcomings. Future research directions, including cutting-edge neuroimaging techniques and imaging genetics, are discussed.

Keywords: developmental coordination disorder, DCD, dyspraxia, adults, review, MRI, fMRI, DW-MRI, DTI, HARDI, CSD, SPECT, functional transcranial Doppler (fTCD) ultrasound, neuroimaging, individual differences, co-occurring neurodevelopmental disorders, comorbidity, genetics

1. Introduction

Developmental coordination disorder (DCD) is a common, but under-recognised neuro-developmental disorder affecting the ability to acquire motor skills, to plan motor actions and to perform actions in motor co-ordinated fashion. According to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) [1], there are four diagnostic criteria for DCD. First, the impairment is characterised by significantly lower than expected (given a person's opportunity for learning and

using a skill and chronological age), acquisition and execution of coordinated motor skills. Second, this motor deficit significantly interferes with the activities of every-day life, academic achievements and occupational and recreational activities. Third, DCD symptoms have their onset in early development. Fourth, deficits in motor skills are not better accounted for by intellectual or visual deficits, or neurological impairments, such as degenerative disorder, cerebral palsy, muscular dystrophy, multiple sclerosis or Parkinson's disease, which affect movement.

Different prevalence rates of DCD have been reported; however, perhaps the most reliable are the results from a large UK population study of 6990 7- to 8-year-old children [2]. This study revealed a prevalence of 1.7%. An additional 3.2% of children were identified as having 'probable DCD' by using broader cut-off criteria on tests of motor coordination and activities of daily living. Males are more often affected than females, with the male to female ratio ranging from 2:1 to 7:1 [1].

Until recently, motor-coordination difficulties in childhood were thought to be typically outgrown in adulthood. However, it is estimated that approximately 75% of those diagnosed with DCD will continue to exhibit motor problems into adulthood [3, 4]. Indeed, studies on DCDAs [5–18] demonstrate that they perform significantly worse than control participants (CPs) on various motor tasks. If one pauses for a moment and considers that the only way humans can affect the world around them is through movement (except for sweating) [19], which is crucial for communication, speech, gesture, sign-language, writing, walking, lifting, etc., it becomes obvious that difficulties with movement will cause a particularly acute deficit in a person who needs to interact with people and the surrounding world. According to the Dyspraxia Foundation [20], the range of motor deficits in DCDAs is wide, including fine motor difficulties (e.g. dressing, handwriting, sewing, putting on make-up, shaving and DIY tasks), gross motor difficulties (e.g. riding a bike, running, engaging in sports, driving a car and dancing), spatial awareness, difficulties with balance and postural control, as well as difficulties with actions which require precise timing, such as catching (e.g. a ball) and keeping up with rhythm. DCDAs also exhibit executive functioning problems in everyday life, such as difficulties organising, managing money, planning ahead and finding things in their room [21]. A glimpse of the fact that DCD adversely affects many areas of DCDA's lives is portrayed below using quotes by DCDAs.

> 'All my life I had assumed I was just "wrong" somehow. Maybe I was just stupid and lazy but was too stupid to see it. Others seemed to be better at things and I was sick of being laughed at or put up with and patronised. I hated being the one who would be slowing others down or not acting how they thought I should act. I spent much of my life just trying my best to physically catch up with other people…' Ruth [20].

> 'My handwriting is dreadful and it takes ages to produce anything legible. It is part of my massive problem in taking notes …' Aileen [20].

> '… When I think of PE I think of being laughed at and being incredibly self-conscious for the obvious reason that PE means moving in front of other people…' Mary [20].

> 'I find it hard to hold my nephew comfortably for us both. I also get overwhelmed when he plays up. […]. Spatial awareness is worse when he jumps on me and demands to be swung around etc.' Chris [20].

Impaired motor skills in DCDAs, crucial for daily activities, have been found to be associated with lower quality of life satisfaction [22–24], difficulties with sleep, higher

levels of fatigue, low self-esteem [25], depression [23, 25–27], higher anxiety [23, 26, 27], difficulties with interpersonal relationships [28], negative outcomes of education and employment [28], low participation in daily life [24] and negative consequences, but a greater ability to use coping strategies than earlier in life [29]. A need for early identification and intervention to prevent the emergence of secondary consequences was underscored [30]. Also increasing awareness of motor difficulties in DCDAs prompted researchers to start developing screening tools for DCDAs [31, 32].

Behavioural genetic studies [33, 34] reported a high heritability estimate for DCD of approximately 70%. A twin/sibling study [27] reported that approximately 0.5 of the variance in coordination difficulty in DCDAs is explained by genetic (and shared environmental) influence. Fliers et al.'s study [35] of sibling pairs with motor problems and ADHD reported a familial component of motor difficulties (comprising genetic and environmental effects) of 0.47 (rated by parents) and of 0.22 (rated by teachers). Moving on to findings from molecular genetics, a genome-wide association study (GWAS) [36] reported no significant findings. However, further analysis showed enrichment of genes for motor neuropathy and genes involved in neurite outgrowth and muscle functions. Among the highest ranked genes was *CHD6,* causing motor coordination problems in mice. These findings are certainly encouraging, but caution needs to be exercised here, because this study focused on participants with ADHD, who also exhibited motor coordination problems; therefore, they may not necessarily hold for participants with DCD. A more recent molecular genetics study [37] was the first to investigate the proportion of heritability in DCD attributed to copy number variations (CNVs—the deletion and duplication of genetic material; an increased burden of large CNVs is associated with autism, intellectual disability and schizophrenia). The results (based on 82 Canadian children with DCD, categorised into four groups—(1) pure DCD, (2) DCD + Reading Disorder, (3) DCD + ADHD, (4) DCD + ADHD + Reading Disorder and 2988 CPs) revealed an increased rate of large and rare genic CNVs and an enrichment of duplications spanning brain-expressed genes and genes previously implicated in other neurodevelopmental disorders. Some cases had a *de novo* (present for the first time) rare CNV, some inherited CNVs (64% of which came from a parent who also had a neurodevelopmental disorder). These results underscore a genetic basis for DCD and suggest that there may be shared susceptibility genes for DCD and other neurodevelopmental disorders.

DCD, similar to other neurodevelopmental disorders, poses a public health concern, but the neuropathological mechanisms underlying DCD are unknown. Analogous to other developmental disorders (e.g. developmental dyslexia and ADHD), DCD is a heterogeneous disorder [38, 39] with complex and varied manifestations. Neuroimaging studies promise new insights into this disorder. Several reviews have recently been published on neuroimaging studies on children with DCD [40–44], but not on adults. Therefore, the aim of this communication is to review neuroimaging publications involving DCDAs with the hope that they will uncover the endophenotypes of mature brain systems affected by DCD.

2. Method

Bibliographic searches of the PubMed and Web of Science databases were conducted to identify papers published before June 2019. The search terms included the following: 'adults', 'developmental coordination disorder', or 'DCD', or 'developmental dyspraxia', and either 'neuroimaging', 'ERPs', 'TMS', 'DW-MRI', 'DTI', 'fMRI', 'MRS', 'VBM', 'MRI', 'SPECT', 'MEG' and 'PET'. A total of 7 studies met the inclusion criteria (peer-reviewed studies published in English, adult participants

(≥18 years old) with DCD or well defined probable DCD who met the DSM-5 criteria for DCD, usage of at least one neuroimaging method).

2.1 Neuroimaging techniques used in the reviewed studies

For clarity, a brief description of neuroimaging techniques used in the reviewed studies is presented below.

The single-photon emission computed tomography (SPECT) imaging technique relies on the delivery of a gamma-emitting radioisotope (usually through injection to the bloodstream) into the participant. Blood flow in the capillaries of the imaged brain regions are indicated by emissions from the radionuclide. SPECT is limited by the lack of a direct measure of metabolism; however, cerebral perfusion and metabolism are closely coupled under the majority of pathologic and normal circumstances. The most common SPECT brain function measure is regional cerebral blood flow (rCBF). Two classes of radiopharmaceuticals are used in SPECT imaging: the diffusible tracers (e.g. ^{133}Xe) and the static tracers (e.g. ^{99m}Tc-ECD). The spatial and temporal resolution are better for the latter (7 mm and 20 s) than for the former (12 mm and 2 min). As SPECT uses ionising radiation, it cannot be used for experimental studies with children and for longitudinal designs, which are particularly important when studying a developmental disorder, such as DCD.

Structural magnetic resonance imaging (MRI) produces high-resolution images of the brain, with clearly distinguishable white and grey matter, fibre tracts and ventricles. It is characterised by relatively good spatial resolution such that brain structures, including subcortical structures much smaller than 1 mm, can be resolved with this method. See also Section 4.4 for more details.

Functional magnetic resonance imaging (fMRI), similar to SPECT and PET, does not directly measure neural events, but metabolic changes which are correlated with neural activity. fMRI exploits the fact that when neurons become active in a given brain area, an increase of the blood flowing to this region occurs. fMRI uses magnetic resonance imaging to measure brain activity by measuring the ratio of oxygenated to deoxygenated haemoglobin, and this value is referred to as the blood-oxygen-level-dependent (BOLD) signal. In an experimental task, brain activity is usually measured, relative to a control task. fMRI has a relatively good temporal resolution of seconds to hundreds of milliseconds and spatial resolution of 4–5 mm. See also Section 4.4 for more details.

Diffusion-weighted magnetic resonance imaging (DW-MRI) relies on the diffusion of water molecules *in vivo* to generate a contrast in magnetic resonance images. Molecular diffusion in tissues reflects interactions with membranes, macromolecules and fibres. Water molecule diffusion allows discovery of microscopic characteristics of brain tissue in a diseased or normal state. Diffusion tensor imaging (DTI) is a special type of DW-MRI. One set of questions which can be asked with DTI relates to the microstructural properties of tissues which are hypothesised to be altered in a given disease or developmental disorder. Important parameters here are the parameters reflecting the total amount of diffusion (apparent diffusion coefficient, ADC) or the fractional anisotropy (FA), defined as a scalar value between one and zero that specifies the degree of anisotropy of a diffusion process. 'One' means that diffusion takes place exclusively along one axis and is completely restricted along all other directions. 'Zero' denotes that diffusion is isotropic (unrestricted or equally restricted) in all directions. Another measure commonly used in DTI studies is mean diffusivity (MD), which is defined as a sum of the diffusivity along the principal axis (axial diffusivity) and the diffusivities in the two minor axes, divided by three. It needs to be pointed out that these measures are sensitive to many different tissue properties, such as axonal density, degree of myelination and axonal

ordering. Furthermore, these measures are not specific to any one of them and this causes difficulties in interpretation of the results [45].

Although DTI is still most commonly used, it is characterised by serious limitations (for more details see Section 3.5). Therefore, recent developments have focused on the high angular resolution diffusion imaging (HARDI) data acquisition strategy. HARDI data acquisition differs only from standard DTI acquisition in which a larger number of unique diffusion-weighting gradient directions are employed, possibly utilising a larger b-value than required for optimal DTI acquisition. Importantly, HARDI is a technique of DW-MRI data acquisition that is necessary for methods, such as constrained spherical deconvolution (CSD) - the goal of which is to resolve the problem of the presence of multiple fibres (crossing fibres) in a single voxel (see Section 3.5, for more details).

It should be noted that structural MRI, fMRI and DW-MRI are all performed using a MRI scanner which (in contrast to PET and SPECT) does not use ionising radiation and can be used with children and in longitudinal designs.

Transcranial magnetic stimulation (TMS) is a neurophysiological technique used to stimulate the brain rather than record electrical or metabolic activity. A special coil is placed on the surface of the skull and the magnetic field passes through the skin and scalp and induces a physiological current that causes firing of the neurons. Placing a TMS coil over the hand area of the motor cortex causes (involuntary) activation of the muscles of the fingers and wrist. TMS is also used to induce temporary 'virtual lesions' by disrupting the sensory and cognitive processing of a given brain area. The consequences of the stimulation are used to shed light on the normal function of the 'lesioned' brain region, analogous to the logic of lesion studies. TMS does not use ionising radiation. The primary activation can be limited to approximately 1–1.5 cm^3; however, downstream effects also occur.

Functional transcranial Doppler (fTCD) ultrasound is a method that allows the non-invasive registration of intracranial blood flow parameters during the performance of a cognitive task. It utilises pulse-wave Doppler technology for registering blood flow velocities in the posterior, middle and anterior cerebral arteries. Analogous to other neuroimaging techniques, it is based on the close coupling between neural activation and regional cerebral blood flow changes. Because of a continuous monitoring of blood flow velocity, fTCD has better temporal resolution than fMRI.

It needs to be pointed out that the neuroimaging methods introduced above are subject to gradual improvement, with regard to their temporal and spatial resolution, as well as other characteristics. For more details on neuroimaging techniques, see [46–50].

3. Results

The following studies are included in this review: a case study involving functional and structural neuroimaging (MRI and ^{99m}Tc-ECD SPECT), four functional imaging studies (one fMRI, two TMS and one functional transcranial Doppler (fTCD) ultrasound) and two structural studies (based on DTI and HARDI with CSD)). The results were statistically significant relative to CPs. The focus is first on the case study, then on the functional imaging studies and finally on the papers on structural imaging. See also **Table 1** for the main characteristics of the reviewed studies and **Figure 1** for a summary of the imaging findings.

3.1 SPECT findings

A study using MRI and ^{99m}Tc-ECD SPECT [51] investigated a 19-year-old left-handed woman who was diagnosed with DCD at the age of 14. She was also

Study	Neuroimaging technique	Task	DCDAs[1]		CPs[2]		DCDAs and CPs	Brain areas	Findings
			N (N of males)	Mean age in years (SD)/ range	*N* (N of males)	Mean age in years (SD)/ range	Exclusion and inclusion criteria[32]		
Marien et al. [51]	^{99m}Tc-ECD SPECT Structural MRI	n/a	Case study (0)*	19	15 (8)	45–70	Diagnosed with DCD at the age of 14	31 ROI[33]	*SPECT:* Person with DCD (vs CPs): sig.[3] ↓[4] perfusion in R[5] cerebellar hemisphere and a hypoperfusion in L[6] medial prefrontal region and R occipital area *MRI:* a slight anterior/superior asymmetry of vermal fissures consistent with rostral vermis dysplasia (type 1a)
Kashuk et al. [52]	fMRI 3 T Block design (Four blocks based on difficulty)	Motor imagery	12** (5)	24.5 (7.6) 18–40	11 (6)	26.7 (5.5) 19–36	*DCDAs:* No self-reported diagnosis of ADHD, intellectual disability, autism, Asperger's Syndrome, history of neurological disease or head injury; normal cognitive and intellectual function (assumed); a standard score on MAND[7] ≤ 85 (15th percentile) on either: total score or fine or gross motor components; a score of ≥8 on the child (ADC[8]) and a score of ≥30 on total score on ADC *CPs:* a standard score on MAND ≥85 (15th percentile) on either: total score or fine, or gross motor components	Whole brain	*DCDAs (vs CPs):* sig. ↓ activation (with increasing difficulty of the task) in: L superior parietal lobe, R and L middle frontal gyrus, R and L occipital lobe/Cuneus and L cerebellar Lobule VI
He et al. [53]	Single-pulse (sp) TMS (to locate the site of the L hPMC[9]); paired-pulse (pp) TMS MEP[10]	*Intrahemispheric cortical inhibition:* CSP[11] recording, Ps[12] asked to keep voluntary muscle contraction at ~20% of MVC[13], measured by the grip force	8** (4)	23.75 (1.67) 21–32	10 (6)	26 (4.24) 21–26	*DCDAs:* No formal diagnosis of DCD, but met all the criteria according to DSM-5; ≤15th percentile for total motor composite of BOT-2[15]; ≥25 on ADC	hPMC	*DCDAs (vs CPs):* no sig. Dif.[16] on: mean SICI[17], LICI[18] and CSP Sig. ↓ interhemispheric hPMC cortical inhibition (sig. ↓ mean ISP[19])

Study	Neuroimaging technique	Task	DCDAs[1]		CPs[2]		DCDAs and CPs	Brain areas	Findings
			N (N of males)	Mean age in years (SD)/ range	N (N of males)	Mean age in years (SD)/ range	Exclusion and inclusion criteria[32]		
		Interhemispheric cortical inhibition: ~ 3 s before each pulse, Ps asked to perform 100% of MVC of their L hand; Ps asked to relax their hand during ITI[14]					for total score and ≥6 for the child score; *CPs:* > 20th percentile for total motor composite of the BOT-2 *Both groups:* normal intelligence (assumed); free of any self-reported medication or neurological impairments		Sig. correlation between mean ISP ratios and performance on the BOT-2 manual dexterity subtest across the groups
Hyde et al. [54]	TMS MEPs (recorded from R FDI[20] via electromyography) Stimulation latency: 50, 400 and 650 ms	Novel adaptation of HLT[21]; no instructions to Ps cueing MI[22] Ps fixated on the cross until an image of a hand appeared; they answered (using eye-movements) whether the displayed hand was L and R	8** (3)	24.29 (4.49) 20–33	21 (11)	25 (4.82) 18–36	*DCDAs:* No formal diagnosis of ADHD, dyslexia or ASD; met DSM-5 criteria for DCD; BOT-2 ≤15th percentile (except one participant's score = 16th percentile); ADC total score ≥25; ADC child score ≥6 *CPs:* age-appropriate motor abilities >20th percentile on BOT-2 *both groups:* normal intelligence (assumed); free from self-reported medication and neurological impairment	L hPMC	DCDAs who used MI (vs CPs who used MI): (1) no ↑ in corticospinal excitability; (2) a lack of change in R hand MEPs following single-pulse TMS to the L hPMC during HLT performance (relative to baseline); (3) first study to report that ↓ MI efficiency in DCDAs (vs CPs) was associated with ↓ activity of the L hPMC
Hodgson et al. [55]	fTCD[23] ultrasound	A covert word generation	12** (4)	25.33 (9.01) 18–43	12 (5)	20 (2.66) 18–28	*DCDAs:* formally diagnosed with DCD within the 10 years previous to the date of the experiment; ADC: sig. motor difficulties in childhood; scored above the diagnostic threshold on self-reported difficulties as an adult *CPs:* not specifically matched for age and gender to DCDAs	Whole brain	DCDAs (vs CPs): a sig. ↓ L lateralisation pattern for covert speech production (while no behavioural deficits for speech)

Study	Neuroimaging technique	Task		DCDAs[1]		CPs[2]		DCDAs and CPs	Brain areas	Findings
				N (N of males)	Mean age in years (SD)/ range	*N* (N of males)	Mean age in years (SD)/ range	Exclusion and inclusion criteria[32]		
								Both groups: not diagnosed with other neurological disorders; English as a first and primary language		
Williams et al. [56]	DTI	n/a		12** (6)	24.5 (7.6) 18–40	11 (5)	26.7 (5.5) 18–40	*DCDAs:* No formal DCD diagnosis; MAND score on total or component scores of ≤85 *CPs:* ≥85 on MAND score on total or component scores *Both groups:* No diagnosis of ADHD, autism or Asperger's syndrome and intellectual disability; no history of neurological disease, no head injury	ROI: R CST[24], L SLF[25], L internal capsule and R ILF[26]	*DCDAs* (vs CPs): (1) sig. ↓ FA[27] in R CST and L SLF; (2) sig. ↓ MD[28] in L internal capsule and R ILF No sig. Dif. between the groups on FA in the L internal capsule; all four ROI correlated with the total SS from the MAND; ↓ FA values in the R CST and L SLF associated with poorer motor ability ↓ MD values in the L internal capsule and R ILF also linked to poorer motor ability
Hyde et al. [57]	HARDI[29] MRI 3 T CSD[30] model and DTI model	n/a		7** (3)	23.29 (4.31) 18–46	12 (9)	26.16 (7.64) 18–46	*DCDAs:* met the DSM-5 criteria for DCD; (one participant had a previous diagnosis of DCD); scores <16th percentile for a summary of BOT-2 total; ≥25 on total score and ≥6 on child score on ADC *CPs:* > 20th percentile on BOT-2; free of self-reported medical or neurological impairment *Both groups:* No diagnosis of ADHD or similar neurodevelopmental disorder	Whole brain deterministic CSD and DTI tractography ROI: L and R CST, L and R SLF	*CSD model:* DCDAs (vs CPs): (1) sig. ↓ mean AFD[31] in the L SLF; (2) a trend for ↓ tract volume of the R SLF *DTI model:* no differences between the groups in R and L SLF microstructure *Both models:* No differences between groups in L and R CST microstructure Sig. moderate positive correlation between mean AFD of the L SLF and total BOT-2 percentile score

[1]*Adults with developmental coordination disorder.*

[2]*Control participants.*

[3]*Significant.*

[4]*↓ lower/decrease and ↑ higher/increase.*

[5]*R, right.*

[6]*L, left.*

[7]*McCarron assessment of neuromuscular development.*

[8]*Adult developmental co-ordination disorders/dyspraxia checklist.*

[9]*hPMC, (human) primary motor cortex.*

[10]*Motor-evoked potential, measured by electromyography (EMG) electrodes.*

[11]*CSP, cortical silent period.*

[12]*Participants.*

[13]*Maximal voluntary contraction.*

[14]*Inter-trial intervals.*

[15]*Bruininks–Oseretsky test of motor proficiency.*

[16]*Difference/s.*

[17]*SICI, short-interval cortical inhibition.*

[18]*LICI, long-interval cortical inhibition.*

[19]*ISP, ipsilateral silent periods.*

[20]*First dorsal interosseous.*

[21]*Hand laterality task.*

[22]*Motor imagery.*

[23]*Functional transcranial Doppler (fTCD) ultrasound.*

[24]*CST, corticospinal tract.*

[25]*SLF, superior longitudinal fasciculus.*

[26]*ILF, inferior longitudinal fasciculus.*

[27]*27FA, the fractional anisotropy.*

[28]*MD, mean diffusivity.*

[29]*HARDI, high angular resolution diffusion imaging.*

[30]*CSD, constrained spherical deconvolution.*

[31]*AFD, apparent fibre density.*

[32]*Additional exclusion criteria also applied, for instance Ps with magnetic or metallic materials within their body, or suffering from claustrophobia, were not examined using the MRI scanner.*

[33]*Not fully specified.*

*Diagnosed also with developmental apraxia of speech.

**Co-occurring developmental disorders not reported.

Table 1.
Neuroimaging studies on DCD in adults.

diagnosed with developmental apraxia of speech. At the age of 19 years, she still had difficulties in establishing social contacts and was characterised by emotional instability and inability to maintain close relationships because of low self-esteem. Her IQ was within the normal range, but she performed better on VIQ than on PIQ (WAIS-III). She exhibited difficulties with block design (WAIS-III) and with copying the Rey-Osterrieth figure. She also had visual perception problems, distorted visual-motor integration skills and visual-motor coordination, as well as impairment of frontal planning and problem solving. There was no evidence of further cognitive deficits. Cerebellar function was tested with the Brief Ataxia Rating Scale (BARS) and revealed mild ataxia, tandem gait was not possible but was normal naturally. Her performance on the lowering of the heel was executed in a continuous axis but the movement was decomposed into several phases. Regarding the finger to nose test, oscillating movements of the hand and arm without decomposition of the movement were recorded. A few articulation errors, oral diadochokinesis and a laboured articulatory setting were noted during motor speech. The patient did not exhibit oculomotor abnormalities.

A quantified ^{99m}Tc-ECD SPECT investigation showed a significant decrease of perfusion in the right (R) cerebellar hemisphere and a hypoperfusion in the R occipital area and left (L) medial prefrontal region. Decreased perfusion in the L cerebellar hemisphere, the vermis, and the R medial prefrontal area only approached significance. Furthermore, structural MRI showed a slight anterior/superior asymmetry of vermal fissures which is in line with rostral vermis-dysplasia (type 1a). It is not clear whether this anatomical abnormality was relevant to the cerebellar functional deficit reported in SPECT examination. According to the authors, cerebellar deficiency would affect the cerebello-cerebral network involved in the execution of planned actions, visual-spatial cognition and affective regulation. On the basis of these findings, the authors concluded that the cerebellum was involved in the underlying causes of DCD.

3.2 fMRI findings

An fMRI mental rotation study by Kashuk and colleagues [52] aimed to ascertain whether adults with probable DCD (pDCDAs; not formally diagnosed with DCD, but who obtained scores on various DCD tests which indicate impairment), compared to CPs, exhibit a reduced ability when engaging in implicit motor imagery, which involves representing movements from an internal perspective, and whether they would exhibit atypical patterns of neural activation. A total of 11 adult CPs and 12 pDCDAs took part in the study. The stimulus images were pictures of R and L hands, shown so that the palm of the hand was facing the participants. They were asked to try to imagine their hand in the position of the displayed hand and decide (by pressing an appropriate button) whether they saw the R hand or L hand. Stimuli were presented in four blocks based on difficulty (Baseline (0°), Easy (40–60°), Medium (80–120°) and Hard (140–160°)). There were no significant between-group differences on response accuracy and time. Therefore, the neuroimaging results were not confounded by between-group differences on these variables. The neuroimaging results revealed significantly lower BOLD signal for increasing angle of rotation for pDCDAs than CPs in the parieto-frontal and occipito-parietal networks, including the R and L middle frontal gyrus, L superior parietal lobe, R and L occipital lobe/cuneus and cerebellar lobule VI. The authors concluded that the underactivation within the frontal, parietal and cerebellar areas may reflect deficient connectivity between areas responsible for the prospective control of movement and action planning. These results could also be interpreted as reflecting
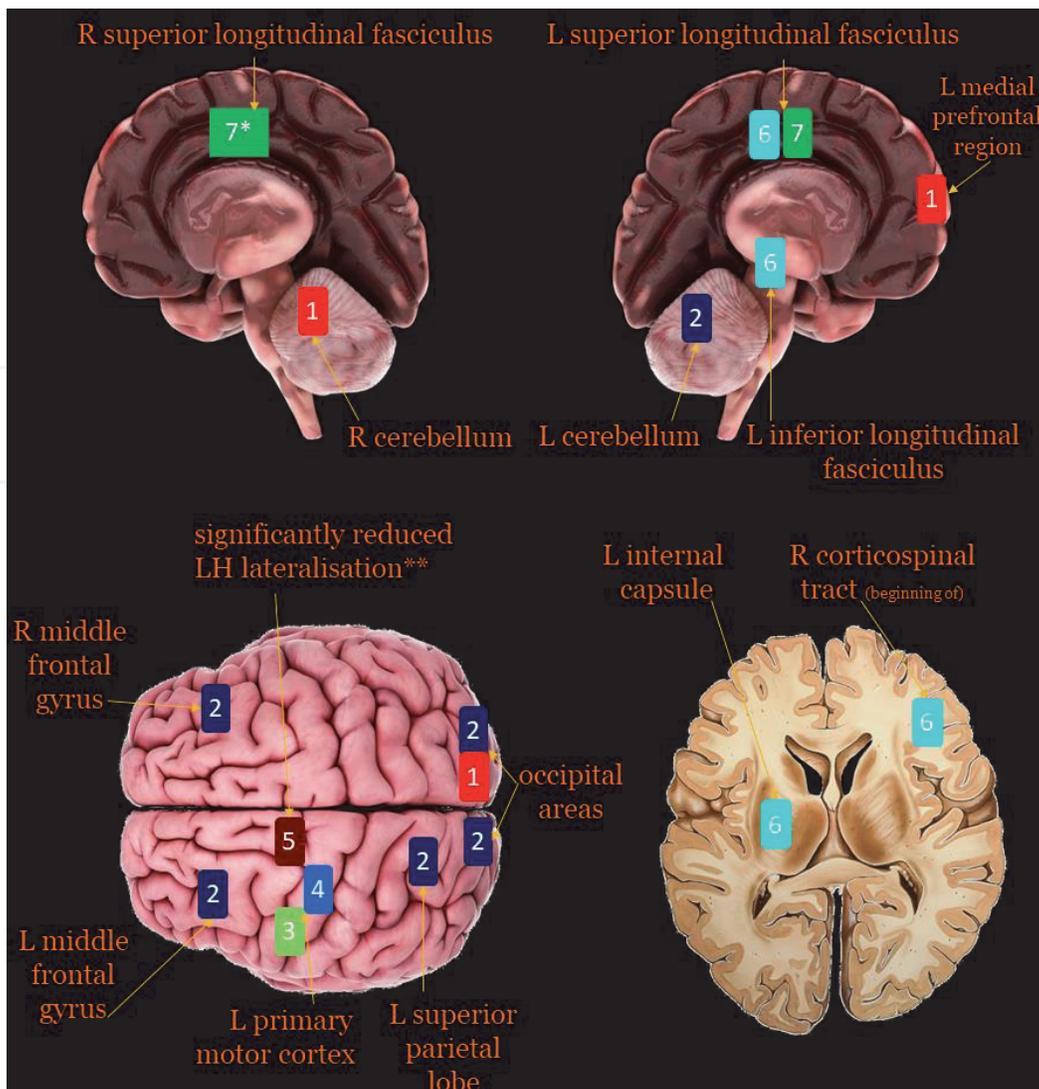
Figure 1.
*Areas of non-typical brain involvement reported in neuroimaging studies of DCDAs vs. CPs displayed on the R and L medial surfaces of the brain, the brain surface viewed from above and the horizontal section of the brain. The numbers in the coloured rectangular shapes denote each neuroimaging study, as follows: 1 = Marien et al. [51], 2 = Kashuk et al. [52]; 3 = He et al. [53], 4 = Hyde et al. [54], 5 = Hodgson et al. [55], 6 = Williams et al. [56] and 7 = Hyde et al. [57]. See **Table 1** for details; * denotes not a significant result, but a trend (with medium-large effect size) for decreased tract volume of the R SLF; ** denotes significantly reduced LH lateralisation in DCDAs vs. CPs.*

deficits within the underactivated areas, or even both interpretations may hold. Further studies, using different neuroimaging techniques, such as voxel-based morphometry (VBM that involves a voxel-wise comparison of the local concentration of grey matter between two groups of participants [58]), DTI (a technique which, additionally to its features described above, allows for the investigation of the anatomical structure of the axon tracts and can provide information on the between-regional anatomical connectivity between different brain areas [48]), or more sophisticated diffusion techniques, such as HARDI (with (CSD) [47]), as well as fMRI, on the same sample of pDCDAs may be able to shed further light here.

3.3 TMS findings

A study by He and colleagues [53] utilised TMS. The authors hypothesised that difficulties found in DCD, such as poor surround inhibition, compromised motor

inhibition and presence of mirror movement, point to underlying problems with the regulation of inhibition within the hPMC. The aim of their study, therefore, was to test the integrity of intrahemispheric and interhemispheric cortical inhibition in the hPMC in DCDAs, as compared to CPs. A battery of single-pulse TMS and paired-pulse TMS protocols, normally employed to measure interhemispheric and intrahemispheric cortical inhibition, was used. Eight DCDAs and 10 CPs participated in the study. The results showed that, in contrast to the predictions, intrahemispheric cortical inhibition in the hPMC appeared to function normally in DCDAs. There were no group differences on mean SICI ratios (short-interval cortical inhibition—considered to activate fast-acting GABA$_A$ receptors), mean LICI ratios (long-interval cortical inhibition—presumed to activate relatively slower-acting GABA$_B$ receptors) and mean CSP ratios (cortical silent period—thought to reflect GABA receptor activity). On the other hand, congruent with the hypothesis, interhemispheric hPMC cortical inhibition was significantly reduced in DCDAs, as compared to CPs. DCDAs exhibited significantly smaller mean ISP ratios (ipsilateral silent periods—assumed to be dependent on GABA$_A$ and GABA$_B$ receptor activity), compared to CPs. Furthermore, a significant correlation between mean ISP ratios and performance on the BOT-2 manual dexterity subtest across groups, was found, indicating that reduced interhemispheric cortical inhibition in the DCDAs (and CPs) was associated with lower scores on subtests that involve bimanual coordination. It is not clear why intrahemispheric cortical inhibition in the hPMC appeared to function normally in DCDAs. A study by He and colleagues [53] was the first to provide some evidence in support for a hypothesis that regulation of GABAergic activity within the hPMC may be atypical in DCDAs. The authors argued that whereas the above results suggest that the GABAergic processes within the inactive contralateral hPMC may be preserved in DCDAs, further investigations are needed to ascertain whether modulation of these processes, flexibly, during movement, to support the suppression of unwanted movement, is possible by DCDAs, as is observed in healthy adults. Finally, as the authors focused on only the dominant (L) hemisphere, future work is needed to test cortical inhibition of the non-dominant (R) hemisphere.

A study by Hyde et al. [54] also using TMS, focused on the hPMC and aimed to test whether decreased ability in motor imagery (MI) in DCDAs, documented in behavioural studies (e.g. [59]), was associated with atypical activation in the hPMC. Single-pulse TMS was applied to the L hPMC under the assumption that changes in the contralateral hand motor-evoked potentials (MEPs) reflect activity in the hPMC. Six DCDAs and 15 CPs performed a novel adaptation of the classic hand laterality task (HLT), where participants' gaze is monitored by eye tracking and they respond visually. Single-pulse TMS was administered to the hand node of the L hPMC at three different time intervals, post stimulus presentation during the HLT. MEPs were recorded from the R first dorsal interosseous (FDI) using electromyography (a technique for registering the electrical activity produced by skeletal muscles). The results showed that 75% of DCDAs and 71% of CPs engaged in MI during the HLT and there was no significant difference between the groups; only these participants were included in the analysis because modulation of the hPMC during HLT performance is considered as being dependent on the MI strategy. MI users with DCD were significantly less efficient than MI using CPs. In contrast to CPs, no evidence of increased hPMC activity during MI was detected in DCDAs. The authors concluded that their data were consistent with the hypothesis that inefficient MI in DCDAs may be due to underactivation of the hPMC. It would be of importance to investigate the structural and functional characteristics of the hPMC in DCD using structural MRI (with VBM) and functional imaging methods, such as fMRI and MEG in the same sample of DCDAs. Furthermore, as pointed out by the

authors, future work also needs to address the role of downstream mechanisms in the deficient activity in the hPMC in DCDAs.

3.4 fTCD ultrasound findings

A study by Hodgson and colleagues [55] used fTCD ultrasound. Given research evidence suggesting that the typical pattern of hemispheric specialisation is altered in individuals with neurodevelopmental disorders, such as SLI and dyslexia, the authors assessed whether DCDAs exhibit reduced L hemisphere lateralisation for speech production compared to CPs [55]. Twelve DCDAs and 12 CPs performed a covert word generation task while undergoing fTCD. All DCDAs had been diagnosed with DCD within the 10 years previous to the date of experimental examination. The results showed that DCDAs exhibited a significantly reduced L lateralisation pattern for the speech production task, relative to CPs, with no behavioural deficits for speech. Therefore, the fTCD results could not have been confounded by behavioural speech deficits. Following the results of a study which reported that CPs with the *KIAA0319/TTRAP/THEM2* gene variants [60] (identified as increasing the risk of developmental dyslexia) exhibited a reduced L hemispheric asymmetry of the superior temporal sulcus (during a reading task), it may be possible in future research to link specific gene variants to the significantly reduced L lateralisation pattern for speech production reported in DCDAs [55], using an imaging genetic approach.

3.5 DW-MRI findings

A DTI study by Williams and colleagues [56] investigated whether white matter microstructure alterations reported in children with DCD [61–63] were also present in pDCDAs. Twelve pDCDAs and 11 CPs underwent DTI. The results revealed that the pDCDAs (in comparison with CPs) exhibited significantly lower FA in the superior longitudinal fasciculus (SLF) and the corticospinal tract (CST). Furthermore, pDCDAs (in comparison with CPs) had lower MD in the inferior longitudinal fasciculus (ILF) and internal capsule. These results suggest that there were significant (most likely persistent throughout the life span), neurobiological alterations in the microstructural properties of the white matter in these white-matter structures between pDCDAs and CPs. The result of reduced FA in the SLF is congruent with the findings reported for children by Langevin and colleagues [62]. In contrast, the finding of lower FA in the CST tract does not replicate previous findings for children [63]. However, it has to be born in mind that given the considerable heterogeneity of DCD, the results are not directly comparable because these studies tested different individuals who also markedly differed in age range (18–40 years [56] and 8–12 years [63]). As DTI (or (HARDI)) with (CSD) is not an invasive method, and does not use ionising radiation, it would be desirable to clarify these differences in a longitudinal study which starts in childhood and continues into adulthood.

All studies on white matter organisation in DCD participants relied on DTI. However, as DTI uses a single tensor to estimate fibre orientation within a voxel, it is only able to resolve a single fibre orientation per voxel and cannot represent multiple fibres in a single voxel (the 'crossing fibre' problem). Because fibres cross in up to 90% of white matter voxels [64], DTI technique is prone to providing incorrect reconstructions or spurious white matter tracts and therefore caution is needed when interpreting DTI results [65]. Bearing in mind this criticism, Hyde and colleagues [57] reported a pilot study, exploring CSD—a method robust to the issue of 'crossing fibres' that calculates apparent fibre density (AFD)—a metric of

intra-axonal volume fraction [66], with higher values likely indicating greater axon diameter or local axon count [67]. The white matter tissue organisation of the sensorimotor tracts in DCDAs was examined using CSD. Seven DCDAs and 12 CPs underwent HARDI. The R and L CST and SLF were delineated and all tracts were then generated using both CSD and DTI tractography. DCDAs demonstrated significantly decreased mean AFD in the L SLF relative to CPs and a trend for decreased tract volume of the R SLF, on the basis of the CSD model. When using the DTI model, no between group differences were found in SLF microstructure. Furthermore, there were no between group differences in the bilateral CST microstructure regardless of the diffusion model. Finally, a significant moderate positive correlation between mean AFD of the L SLF and total BOT-2 percentile score was found, revealing a relationship between motor performance and diffusion metrics. The authors interpreted the results as being consistent with the hypothesis according to which the motor impairment observable in DCD may be due to white matter abnormalities in sensorimotor tracts, especially in the SLF. More specifically, they emphasised that their results suggest that DCDAs (in comparison to CPs) are characterised by decreased axon diameter or decreased axon count in the L SLF and in R SLF (a non-significant trend). As the authors pointed out, this is of interest because smaller axonal diameter has been linked to slower axonal conduction. The results from Hyde and colleagues' study based on CSD seem very promising. However, the authors did not replicate the CST abnormality found in the study reported by Williams and colleagues [56], and relied on a small sample of participants; therefore, the results of Hyde and colleagues' study need to be replicated with a larger sample of DCDAs.

3.6 Summary and critique

Summarising, the neuroimaging results revealed functional abnormalities in the R cerebellar hemisphere, L medial prefrontal hemisphere and R occipital region [51], L superior parietal lobe, bilateral middle frontal gyrus, bilateral occipital lobe/ cuneus and L cerebellar Lobule VI [52]. Structural white matter abnormalities were found in the R CST and L SLF, L internal capsule and R ILF [56] and in the L SLF with a trend for abnormality in the R SLF, with no abnormality in the microstructure of the CST [57]. Furthermore, DCDAs exhibited significantly reduced interhemispheric cortical inhibition within the hPMC [53], lack of evidence of increased hPMC activity during a motor imagery task [54] and a reduced leftwards brain asymmetry for speech [55]. These results suggest that, similar to neuroimaging findings on children with DCD [40], DCD manifests as a complex neurodevelopmental disorder in DCDAs. DCDAs' unresolved motor problems from childhood persist into adulthood and are associated with functional and structural brain abnormalities.

However, a majority of reviewed studies have shortcomings. First, most of the studies relied for convenience on small, unrepresentative and underpowered samples which are problematic, especially when dealing with a heterogeneous disorder, such as DCD; Second, some studies relied on adults with probable DCD, rather than adults with diagnosed DCD, and this may have added to the heterogeneity across the samples. It should be mentioned here that according to the International Clinical Practice Recommendations for DCD [68], presently there are no explicit diagnostic criteria for DCD for adults. DSM-5 mentions adults and it has been interpreted that the same criteria as for children, with small adaptations, may be used for adults [68]. Furthermore, there are no standardised assessments for DCDAs, except for BOT-2 (norms up to 21 years, but only for USA and Germany) and MAND (norms for 18–35 years), but they are more than 20 years old. These factors make

diagnosing DCD in adults difficult. Because the age of some adults with probable DCD, included in the reviewed studies, lies outside the norms for BOT-2 and MAND, the results must be interpreted with caution. Third, gender and age were not tested systematically. These variables are important, because DCD seems to be a disorder characterised by gender bias and important gender differences in DCD were reported by, for instance, studies on environmental factors (see Section 4.5 below); also neuroimaging studies on other developmental disorders, e.g. dyslexia have revealed gender-specific grey matter volume differences [69]. Furthermore, crucial maturation processes take place in brain development in adolescence and adulthood [70, 71]; therefore, age ranges that include young adults and middle-aged adults, reported in more than a half of the reviewed studies, are not advisable cf. [40]. Fourth, most studies have potential confounds because DCD co-occurs with other neurodevelopmental disorders, such as dyslexia and ADHD and many others (for more details see the Section 4.1 below), most of which were not controlled for in the reviewed studies. Fifth, DCD is a heterogeneous disorder; hence, reliance on between-group comparisons might obscure the results for underrepresented cases. Sixth, prenatal and perinatal history (shown to impact neurological findings) was not reported in any of the reviewed studies. Seventh, the studies usually only provide a small number of DCD measures; however, it would be desirable that more extensive testing of motor abilities were included, giving an in-depth description of the nature and severity of the motor difficulties. As there is now growing evidence of cerebellar deficit in DCD, it would also be advisable to test the cerebellar function behaviourally in participants with DCD. Finally, as DCD is a developmental disorder, longitudinal studies are needed to understand the deficits in this disorder—it is likely that manifestations of deficits in DCD will differ in different developmental stages.

Overall, although the neuroimaging studies on DCDAs reviewed above, reported interesting results, the small number of studies, small unrepresentative samples and limited number of neuroimaging techniques indicate that, in comparison to neuroimaging studies on other developmental disorders, neuroimaging in DCDAs is a very young field. Therefore, there is an urgent need for further neuroimaging studies on DCD which would address the above-mentioned shortcomings. Future directions for DCD research, including cutting-edge neuroimaging techniques and imaging genetics, are discussed below.

4. Future directions

4.1 Studies on the underlying causes of DCD

Within the field of DCD research, there is an urgent need for studies which focus on investigating the underlying causes of DCD. The current research indicates that the co-occurrence of neurodevelopmental disorders is most likely more common than cases of 'pure' disorders [72] with up to 70% of children meeting the criteria for at least one other neurodevelopmental disorder [73]. Motor deficits have been associated with a considerable number of developmental disorders, although quite often it was considered to be part of a given disorder, rather than a part of possibly co-occurring DCD [74]. There is growing evidence that DCD co-occurs with many other disorders, such as ADHD (the most frequent co-occurring disorder, in approximately 50% of cases), dyslexia, dysgraphia, speech and language disorder, autism spectrum disorder, visual perception deficit, joint hypermobility syndrome and disruptive and emotional behavioural problems [1]. Furthermore, co-occurrence with other disorders such as specific language

impairment (SLI) [75], developmental apraxia of speech [51] and arithmetic and working memory difficulties [76] was also noted. At present the relationship between DCD and co-occurring disorders is not clear. It should be emphasised here that although efforts were made to control the effects of some co-occurring disorders (e.g. ADHD), the effects of many other potentially co-occurring disorders were not controlled for in the reviewed studies. Therefore, there is an urgent need for future research on the underlying causes of DCD to control for the effects of these either by the exclusion of cases with such disorders or by collecting appropriate data from cases with co-occurring disorders to be entered as covariates in analyses. Otherwise the results would be confounded by the effect of co-occurring developmental disorders and no claims could be made with regard to the effects of DCD. For a similar argument regarding research on developmental dyslexia see [77, 78].

An important issue in investigating the underlying causes of DCD is to use a robust theoretical framework. A single deficit model has been dominant for many years in the research on neurodevelopmental disorders. For instance, according to the internal modelling deficit (IMD) hypothesis [79], the movement difficulties in DCD are due to a deficit in the ability to engage predictive control during planning and executing movements. This is concluded from the evidence on participants with DCD (DCDPs) who, in comparison to CPs, exhibit deficient motor imagery, a smaller amount of anticipatory postural adjustment when initiating movement and slower adjustments to target perturbations during the action of reaching [80]. However, a single deficit model, although parsimonious and relatively easy to test, has limitations. For instance, as underscored by Wilson and colleagues [80], IMD hypothesis is supported, among other results, by behavioural data on effector systems, but deficits were stronger on tasks that involved higher complexity or required more endpoint precision. These indicate that some other deficits may be involved. Furthermore, the results from neuro-imaging studies reported that abnormalities in brain function and structure are also present in areas that do not belong to IMD/MNS (mirror neuron system) networks; for instance, in children with DCD (compared to CPs), significantly lower BOLD in L superior frontal and lingual gyri was reported [81, 82]. Therefore, it may be a fruitful way forward to consider a multiple deficit model (MDM), similar for instance to that proposed for developmental dyslexia [83]. According to MDM, more than one deficit is necessary to cause a given developmental disorder, such as DCD. In contrast to a single deficit model, MDM can account for any more frequent than chance co-occurrence of the neurodevelopmental disorder with another neurodevelopmental disorder.

Another model that needs to be considered here is the recently proposed hybrid (multicomponent) model of motor skill development based on advances in cognitive neuroscience and ecological systems theory [80]. It consists of three components: individual, task and environment. The individual level is most complex and consists of motor abilities, motor and cognitive processes and biological maturation and genetics. Importantly, motor performance emerges from the interaction of these three components (for more details see [80]). This model may prove particularly valuable for longitudinal studies of DCD. Finally, the neural systems hypothesis (NSH) [84] may also prove to be a useful framework for further DCD research. According to this hypothesis, research on developmental disorders can be unified by the claim that their underlying cause is a deficient procedural learning system. The main underlying cause of DCD is classified by NSH as a motor-cortico-striatal deficit. Participants with DCD, who also suffer from verbal dyspraxia (like the person in the case study reported above [51]), might also be classified as having language-cortico-striatal difficulties. It could not be stressed more that discovering

the underlying causes of DCD is of vital importance, not only for gaining insight into this neurodevelopmental disorder but also for designing appropriate interventions.

4.2 Neuroimaging studies using longitudinal designs

The reviewed studies investigated DCD in adults. Such studies are undoubtedly important because through them an insight into the neural correlates of DCD in a mature system is gained. Furthermore, focus on adults with DCD allows one to bypass a potential problem of the presence of the sub-group of children with DCD who 'grow out' of their motor difficulties [56]. However, it is possible that the adult neural system may have been partially or greatly altered due to compensatory mechanisms, as a reaction to brain abnormalities. Furthermore, providing that motor skills (gross and fine) are learned over a relatively protracted period of time, it is likely that brain-based findings are going to be dynamic and change over time. Therefore, as well as continuing research on adults with DCD, there is an urgent need to develop longitudinal neuroimaging studies, starting with infants from families at risk of DCD, so that the developmental trajectory of deficits in DCD can be tracked over time.

4.3 Focus on individual differences in DCDAs

The issue of individual differences is crucial in studying and understanding heterogeneous developmental disorders; however, it is usually (with few exceptions, e.g. [77, 78]) neglected. As stated earlier in this chapter, DCD is a heterogeneous disorder, hence reliance on between-group comparisons (with a group consisting of participants with DCD (DCDPs) being most likely heterogeneous) might obscure the results for underrepresented or rarer cases. Furthermore, the proportion of individuals with DCD having a different profile in a given sample can vary across studies, resulting in non-congruent results. Therefore, a promising way forward in DCD research would be to carry out multiple case studies that focus on individual differences. Another fruitful and more powerful direction would be to compile an extensive test battery to identify sub-groups of DCDPs, as homogeneous as possible, and these in turn may then be compared on dependent variables to CPs or to each other.

4.4 Extending the types of imaging tools used in DCD research

The reviewed studies used structural MRI, SPECT, fMRI, TMS, functional transcranial Doppler (fTCD) ultrasound, DTI and HARDI. This is only a subset of currently available neuroimaging tools, and usage of additional neuroimaging techniques may shed new light on the DCD endophenotype. Given that interesting findings from magnetic resonance spectroscopy (MRS) have been obtained for developmental dyslexia [85] and ADHD [86], it seems promising to use this technique to investigate DCDPs. MRS is the only research tool that allows a non-invasive *in vivo* assessment of neurochemical aspects of a given disorder without using ionising radiation. It obtains a measure of the quality of brain tissues and detects concentrations of specific neuro-metabolites *in vivo*, such as: *N*-acetylaspartate (NAA), *N*-acetylaspartate plus *N*-acetyl-aspartyl-glutamate (tNAA), choline (Cho), creatine (Cr), creatine plus phosphocreatine (Cr + PCr), GABA, glutamate (Glu), glutamine (Gln), glutamate plus glutamine (Glx), myo-inositol (mI), myo-inositol-containing compounds (Ino), freely mobile membrane

phospholipid precursors (free-PME) and freely mobile membrane phospholipid breakdown products (free-PDE). For more details on MRS, see [87].

Findings from investigations using DTI [56] and HARDI (with CSD model) [57] on DCDAs and children with DCD [61–63] that suggest white matter abnormalities and results from an MRS study which revealed that heightened levels of choline are associated with abnormalities in white matter [88], prompt the important empirical question of whether both deficits can be found with HARDI and MRS in the same sample of DCDPs. Furthermore, findings by He et al. [53], discussed above, provide the first evidence in support of a hypothesis that regulation of GABAergic activity within the hPMC may be atypical in DCDAs. Therefore, it would be desirable to explore concentrations of GABA in the hPMC in DCDAs using MRS.

Participants with DCD exhibit poor sensorimotor coordination, which among other processes, involves precise timing and using feedback to respond to changes in the environment [89]. Therefore, neuroimaging techniques with good temporal resolution, such as EEG and MEG combined with rigorous scientific experimental designs, may be able to shed new light on the endophenotypes of DCD. Such investigations look even more promising due to recent developments in MEG where new, advanced pre-processing techniques enable decomposition of the signal into components with their origin inside and outside the head. This increases the signal-to-noise ratio by approximately 100%, enabling therefore even one-trial measurements with the standard MEG systems. Furthermore, a considerable increase of MEG signal-to-noise ratio is now possible thanks to optically pumped magnetometers that allow MEG sensors to get closer to the head [90].

There are emerging findings that neurodevelopmental disorders are associated with structural and functional abnormality within the default mode network (DMN). DMN is a large-scale brain network of interacting brain areas characterised by highly correlated activity with each other. It is activated when individuals focus on internal tasks such as retrieving memories, daydreaming and imagining the future. It is distinct from other networks in the brain. Evidence points to disruptions in the DMN of people with neurodevelopmental disorders, including ASD [91, 92] and ADHD [92]. Therefore, it would be advisable to investigate whether this is also the case for individuals with DCD. DMN seems well suited for usage with participants with neurodevelopmental disorders, such as DCD, because it can be measured with effortless and short resting-state scans and can be performed with any population, including children, and may be used in studies with longitudinal designs.

DMN is one of a number of resting-state conditions identified in the brain and researched. Another line of investigation here is whole-brain resting-state functional connectivity (rsfMRI), a technique used to measure intrinsically organised patterns of spontaneous signal fluctuations across the whole brain. Interestingly, a recent study [93] applied a multivariate data-driven approach (where diagnostic categories were not used) to discover latent components linking a large set of cognitive, clinical and personality measures to whole-brain resting-state functional connectivity patterns across CPs and participants with ADHD, schizophrenia, schizoaffective disorder or bipolar disorder. Three latent components—cognitive dysfunction, general psychopathology and impulsivity were discovered. Remarkably, every component was characterised by connectivity alterations within the somatosensory-motor network and in its connections to the cortical executive and subcortical networks. These results identify three latent components as plausible cross-diagnostic phenotypes, which account for comorbidity across disorders. Interestingly, alterations within the somatosensory-motor network is of importance to all the cross-diagnostic phenotypes. Such an approach should also be fruitful in the investigation of DCD and the co-occurring disorders.

There is growing evidence that DCDPs exhibit difficulties in interpersonal interactions [20, 51]. Currently it is not clear whether this is due to pure DCD or to co-occurrence with ADHD and/or ASD. Such difficulties can lead to social isolation and later to depression. Until recently, there was no easy way to study social interaction with neuroimaging. However, in 2009, a 'two-person neuroscience' (2PN), an approach to study the physiological basis of social interaction, was proposed [94]. One of the main experimental goals of 2PN was to differentiate reactive vs. interactive states of human social interaction by measuring simultaneously brain signals from two participants. As natural social interaction involves exchange of information between the participants at time intervals shorter than 100 ms, brain imaging methods with good temporal resolution, such as MEG or EEG are indispensable. Recently, a first set-up for simultaneous MEG-to-MEG recordings was built [95]. The main strength of MEG over EEG in the simultaneous set up recordings is that the sources of the signals (e.g. brain rhythms modulation) can be identified with higher accuracy. Instead of estimating connectivity between regions of a given participant's brain, hyperconnectivity, a measure of functional connectivity between the brains of two participants, can be calculated. With data obtained from two brains in a simultaneous recording, one can investigate the correlations between the two sets of brain signals without explicit reference to the external events [95]. 2PN certainly therefore seems to offer a promising way forward for investigating participants with DCD where interpersonal relationships are affected. However, it should be emphasised here that these are still early days and the data analysis of 2PN is challenging.

Finally, advances in MRI and fMRI, such as multiband fMRI [96] and high-field MRI [97], promise to increase the spatial and or temporal resolution of these neuroimaging methods, ensuring that they will continually serve as powerful neuroimaging tools for investigating the structure and function of the brain in DCD.

Given the heterogeneity of DCD, it is unlikely that one biomarker for this disorder will be sufficient. Therefore, studies that employ more than one neuroimaging technique, for instance, VBM, HARDI (with CSD model) and fMRI with the same sample of participants with DCD, as mentioned in the context of Kashuk et al.'s [52] study, are urgently needed.

In summary, the advances discussed above offer many new possibilities in DCD neuroimaging research. DCD endophenotypes can be investigated with higher spatial and temporal resolution, their DMN and resting-state functional connectivity can be tested, the concentration of metabolites, especially GABA can be determined and utilising 2PN with simultaneous MEG-to-MEG recordings can shed new light on the interacting DCD brain. Finally, using different neuroimaging techniques with the same sample of DCDPs will allow for asking more precise questions. All of these will increase the chances of elucidating the underlying causes of DCD and reliable biomarkers for DCD.

4.5 Environmental factors in DCD

DCD is a multifactorial disorder in which genetic factors and environmental factors as well as gene x environment interactions play a role. As described above, some efforts were made to discover the genetic factors involved in DCD. The research on the environmental factors that influence DCD is limited. The importance of environmental factors was underscored in DSM-V by introducing the new exclusion criterion for DCD, namely the lack of opportunity for skill learning and use. So far, the following environmental factors have been identified as increasing the risk of developing DCD: lower birthweight (less than 2500 g), being born before 37 weeks of gestation and lower socioeconomic status [2], being born pre-term, being small

for gestational age or being 15 months of age or more at walking attainment [98], prenatal exposure to alcohol [1], Caesarean section, maternal pre-eclampsia and low income [99]. Interestingly, gender differences have been reported. Lower than optimal birthweight was associated with poorer motor outcomes in males, whereas, smoking during early pregnancy and stress during later pregnancy were linked to poorer motor development in females [99]. Future studies need to keep testing and refining the knowledge of environmental risk factors in DCD. The research on the underlying causes of DCD needs to collect data on risk factors for DCD and enter them into the analyses to reduce the number of confounds.

4.6 Genetic research

Neuroimaging studies provide descriptions of endophenotypes, but do not offer an explanation as to what is the underlying cause of a given disorder. For this, researchers need to investigate the genetic basis of DCD. In comparison to research on other developmental disorders, genetic research on DCD is lagging behind. Nevertheless, some promising strides have been published, as described in the introduction. An ultimate goal for future genetic research is to ascertain which variants of which genes are risk factors for developing DCD. One way forward here would be to develop high quality GWAS with large, representative samples. The assumption of GWAS is that common variants underlie common disorders and, therefore, they focus on sampling sites of known common genetic variation. GWAS rely on 'arrays' and they only genotype the pre-defined sites of variation and do not sequence every base. Therefore, GWAS cannot be used for searching for rare or new variants within a genome [100]. As it is likely that both common and rare genetic variations contribute to disorder risk in DCD, genome sequencing technologies would be beneficial. This is because they record both common and rare variants, as well as CNVs. However, it has to be born in mind that this technology remains relatively expensive and, as large samples are necessary, the collection of participants with DCD may need to involve international collaboration.

It is very difficult to ascertain the functional impact of genetic variation; however, mouse models have the potential to make an impact on the understanding of the underlying causes of neurodevelopmental disorders, such as DCD. Initial efforts involving mouse models seem promising [101–103]. More recently, in research in progress, the authors [104] used recombinant inbred lines of mice, 12 BXD strains and parental strains C57BL/6J and DBA/2J to investigate DCD. BXD27 mice, characterised by smaller cerebellar volume, showed motor impairments across different skills; the researchers also plan to collect data from brain imaging, so that more light can be shed on the basis of poor motor learning and coordination in BXD27 mice.

The significance of discovering the variants of genes which are genetic risk factors for DCD cannot be emphasised strongly enough. This would open the door to many further investigations, such as imaging genetics, which provides a bridge between the brain and behaviour. For instance, imaging genetics will allow for linking gene variants to the functional and structural abnormalities of grey matter and structural abnormalities of white matter. Such research is more advanced regarding other developmental disorders, e.g. ADHD and developmental dyslexia [78]. Finally, it needs to be underscored that the biological complexity of DCD cannot be disregarded and genome-wide measurements, together with investigations of individual genes and pathways, are crucial in ascertaining the underlying mechanisms of neurodevelopmental disorders, such as DCD [105]. See also the Sections 4.7 and 4.8 below.

4.7 Neuroimaging intergenerational transmission of brain circuitry

Intergenerational neuroimaging is a relatively recent approach that uses neuro-imaging to test the relationship of neural and cognitive phenotypes between parents and their children. It is based on the fact that there is a transfer of traits from parents to offspring which consists of both non-genetic and genetic influences. The impact of prenatal effects (e.g. parent nutrition and *in-utero* environment), rearing effects and other environmental factors could cause epigenetic changes (changes in gene function in the absence of gene sequence changes) or behavioural changes in the children, which are transmitted intergenerationally [106]. Intergenerational neuroimaging may be a promising way forward in clarifying the ontogeny of complex neurodevelopmental disorders, such as DCD. One way of disentangling inherited factors from pre- and postnatal influences is by utilising the potential of natural cross-fostering designs that take advantage of different types of *in vitro* fertilisation (homologous surrogacy (mother is egg donor and birth mother), donor egg pregnancy (mother is not egg donor but is birth mother) or heterologous surrogacy (mother is egg donor but not birth mother)) [106]. Such designs hold promise to address many crucial questions in DCD research. For instance, what are the intergenerational effects on the brain structure and function, including those involved in coordinated movement? What is the impact of gender-specific effects at the prenatal stage (particularly important as DCD is more prevalent in males than females [1]), including the effects of prenatal testosterone levels on brain development, and gender-specific transmission patterns [107, 108] in movement-related brain circuits in newborns.

4.8 Integrative neuroimaging

As discussed above, an inherent difficulty in the research on neurodeve-lopmental disorders is their heterogeneity. Another stumbling block here is the fact that neurodevelopmental disorders are characterised by pleiotropy [105]. These are some of the most heritable disorders, but simultaneously they also are extremely complex genetically. For instance, a dosage of CNV increases one's risk for multiple diagnosis and conversely, given a single diagnosis of developmental disorder, one can reach it from multiple genetic starting points. Therefore, if one wants to find a biomarker, for instance dyslexia, one immediately carries together a group of different genetic conditions, as defined by their genotype. Because of these obstacles, an alternative approach has been proposed [109–111], namely trying to first under-stand the biology of neurodevelopmental disorders with genetically defined groups, such as those with sex chromosome aneuploidy (SCA) syndrome. This strategy can be helpful because the genetic makeups in SCA syndrome are known. It should be emphasised here that having additional sex chromosomes increases the risk for diverse neurodevelopmental disorders, especially those that impact social function and interaction, as well as language. The SCA model may be used to understand how CNV can cause changes in brain systems relevant to neurodevelopmental disorders. Therefore, the SCA syndrome has become the genetically defined risk model for neurodevelopmental disorders [112].

Taking advantage of the growing number of publicly available molecular and cellular maps available in the standard neuroimaging atlas space, such as the Allen Brain Atlas [113] and BigBrain [114] and structural MRI, it has been reported that patients with increasing X or Y chromosome dosage tend to have disproportionally reduced size of cortical brain surface area, such as L posterior insula, L and R anterior cingulate, L gyrus rectus, R anterior cingulate and R posterior orbital gyrus. These patients also exhibit reduced size of cortical thickness of L and R superior

temporal sulcus/medium temporal gyrus, increased cortical thickness of L medial prefrontal cortex, L and R parahippocampal cortex and R orbitofrontal cortex, as well as increased cortical surface area of L and R precuneus [110]. Furthermore, meta-analysis of brain activation patterns across more than 5000 functional neuroimaging publications has revealed that these areas are involved in the detection and processing of biological motion, language, autobiographical memory, reward, affect and interoception [110]. These cognitive domains seem relevant to social functioning and language. It is important to mention that DCDPs exhibit, among other things, difficulties with language and social functioning [20], but it is not clear whether these are due to co-occurrence with other developmental disorders, such as SLI and ASD. Young children (but not adults) with DCD exhibit a specific deficit in coherence sensitivity to motion relative to form [115], but it has to be born in mind that these data are from a cross-sectional study; a subset of children with dyslexia and autism also exhibited a deficit on the motion coherence task [116]. Additionally, after controlling for brain size, patients with increasing X or Y chromosome dosage also tend to have a disproportionally reduced size of cerebellum, pallidum and amygdala [117–119]. As discussed above, cerebellar abnormalities have been reported in neuroimaging studies involving DCDAs [51, 52] and children with DCD [82, 120, 121], but also other developmental disorders, such dyslexia [77, 78, 122] and ADHD [123]. Furthermore, studies on children with DCD have revealed functional abnormalities in the basal ganglia and pallidum [124, 125].

A question that has arisen here is why some brain regions get altered when a patient has an additional sex chromosome and others do not. An answer to this question may provide an insight into the disease mechanism. Recent studies suggest a transcriptional vulnerability model, for the spatial targeting of brain, changes in disease. Testing this required mapping anatomical change in neurodevelopmental disorders and then aligning these maps with the Allen Institute Adult Human Microarray Dataset [113]. The results showed that the spatial pattern of anatomical change in each disorder is associated with the spatial expression profile for genes found in the causal CNV region [126]. These results support the view that intrinsic gradients of gene expression in the human brain, shape cortical vulnerability when the gene dosage is altered. A subsequent question here was: what principles of cortical organisation were determining these gene expression gradients? In the search for an answer, the authors [126] collected a comprehensive set of single-cell gene expression signatures and used post-mortem data to map expression gradients for each canonical cell class in the human brain. The results revealed specific cell-classes that expressed CNV genes and closely tracked the spatial pattern of cortical disruption in each disorder, e.g. *MAPK1*-expressing inhibitory neurons in del22q11. This line of research seems very promising and it is likely that it will provide valuable insights into the underlying causes of neurodevelopmental disorders, including DCD.

5. Conclusion

The results from the review of neuroimaging studies on DCDAs presented here, have revealed that this research lags behind that for other developmental disorders. The results suggest that DCDAs' unresolved motor problems from childhood persist into adulthood and are associated with functional and structural brain abnormalities, revealing DCD as a complex developmental disorder with abnormalities across different brain regions. In order to make significant progress in future, it is suggested that further research would need to: (1) focus on a robust theoretical framework; (2) investigate the underlying causes of DCD; (3) use neuroimaging

studies based on longitudinal designs; (4) focus on individual differences among DCDAs; (5) extend the types of imaging tools, as well as, if possible, use more than one imaging technique with the same sample of participants with DCD; (6) refine the understanding of environmental factors that increase the risk of DCD and include them in the study design; (7) advance genetics findings on genes, the variants of which increase the risk of developing DCD; (8) focus on neuroimaging intergenerational transmission of brain circuitry; and (9) pursue research on integrative neuroimaging. The current era of incredible technological progress within the field of neuroimaging and molecular genetics must surely result in groundbreaking discoveries in DCD research in the not too distant future.

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Conflict of interest

The author declares no conflict of interest.

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