The relationship between neuroimaging and motor outcome in children with cerebral palsy: A systematic review – Part B Diffusion imaging and tractography

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Abstract

Background

Diffusion magnetic resonance imaging (dMRI) is able to detect, localize and quantify subtle brain white matter abnormalities that may not be visible on conventional structural MRI. Over the past years, a growing number of studies have applied dMRI to investigate structure-function relationships in children with cerebral palsy (CP).

Aims

To provide an overview of the recent literature on dMRI and motor function in children with CP.

Methods

A systematic literature search was conducted in PubMed, Embase, Cochrane Central Register of Controlled trials, Cinahl and Web of Science from 2012 onwards.

Results

In total, 577 children with CP in 19 studies were included. Sixteen studies only included unilateral CP, while none included dyskinetic CP. Most studies focused on specific regions/tracts of interest (n=17) versus two studies that investigated the whole brain. In unilateral and bilateral CP, white matter abnormalities were widespread including non-motor areas. In unilateral CP, consistent relationships were found between white matter integrity of the corticospinal tract and somatosensory pathways (e.g. thalamocortical projections, medial lemniscus) with upper limb sensorimotor function. The role of commissural and associative tracts remains poorly investigated. Also results describing structure-function relationships in bilateral CP are scarce (n=3).

Conclusions

This review underlines the importance of both the motor and somatosensory tracts for upper limb sensorimotor function in unilateral CP. However, the exact contribution of each tract requires further exploration. In addition, research on the relevance of non-motor pathways is warranted, as well as studies including other types of CP.

What this paper adds

- An overview of the current literature investigating the relationship between diffusion MRI based measures of white matter tract integrity and motor function in CP.
- Current gaps and future recommendations to further improve our insights into these structure-function relationships.

Highlights

- In unilateral and bilateral CP, white matter microstructural abnormalities are widespread including non-motor areas.
- In unilateral CP, dMRI reveals a relationship between the microstructural properties of motor and somatosensory tracts and upper limb sensorimotor function.
- The contribution of motor versus somatosensory tracts needs further clarification.
- There are limited studies in bilateral spastic CP and in children with dyskinetic CP.

1. Introduction

Cerebral palsy (CP) is the most common cause of physical disability in childhood with prevalence rates of 2 to 3 per 1000 live births in developed countries (Colver, Fairhurst, & Pharoah, 2014). CP results from a brain lesion during early brain development. It is a heterogeneous disorder expressed by a range of symptoms that can vary in type, location and severity. Unfortunately, CP usually results in a lifelong disability, stressing the need to fully understand its underlying neuropathophysiology.

Structural brain abnormalities have been described in the vast majority of children with CP, and demonstrate that each lesion is different in type, location and extent. Most often structural magnetic resonance imaging (sMRI) is used to identify abnormalities in the brain and is considered the gold standard to support the clinical presentation and confirm the diagnosis of CP (Staudt, 2013). A systematic review by Arnfield et al. (2013) summarized the results of all sMRI studies which related brain lesion characteristics with motor outcomes until the end of 2012 (Arnfield, Guzzetta, & Boyd, 2013). This review identified a relationship between the type of brain lesion, the Gross Motor Function Classification System (GMFCS) and the CP subtype. The review by Arnfield et al. (2013) was recently updated in part A of the current review with the aim of including more population-based studies to strengthen the conclusions made and to gain deeper insights into this complex relationship. Contrary to Arnfield et al. (2013), when including more recent literature (n=58 studies), the relationship between the type of the brain lesion and CP subtype or functional classifications such as the GMFCS and the Manual Ability Classification System (MACS) could not be confirmed (Franki et al. 2019). This discrepancy may be due to differences in the clinical characteristics of the populations investigated and heterogeneity in MRI based classification.

Therefore, part B of this review will focus on more advanced neuroimaging methods, specifically diffusion weighted imaging, which is able to identify and quantify subtle microstructural abnormalities in brain white matter, even in the absence of structural damage on a conventional sMRI (Son et al., 2007). Due to its higher sensitivity, diffusion MRI (dMRI) has the potential to provide further, valuable insights into the underlying neuropathology of motor dysfunction. Diffusion MRI can be used to infer the microstructural properties of neuronal tissue by characterizing the diffusion properties of water molecules. Whilst the technique cannot directly measure tissue integrity, in the case of CP, where white matter lesions are well documented, altered diffusion most likely reflects underlying microstructural abnormality. There are a number of techniques to analyze dMRI data. In the CP literature, studies most commonly apply regional analysis of diffusion tensor imaging (DTI) resulting in quantitative parameters such as fractional anisotropy (FA), mean, radial and axial diffusivity (MD, RD, AD). FA characterizes the degree of tissue anisotropy, being highest in uniformly oriented tissue (e.g. axon bundles). The diffusivity measures reflect the amount of overall diffusion (MD) and diffusion along a given orientation (RD, AD). A lower FA and higher diffusivity may arise during microstructural breakdown, e.g. due to cell loss and demyelination, such as in lesions. In addition to providing quantitative maps of diffusion properties, the orientational information captured by the dMRI signal enables the virtual dissection of fiber tracts non-invasively. These 3D reconstructions serve both as regions of interest and also as the basis for local and global connectivity metrics. Hence, white matter tracts, crucial for motor control such as the

corticospinal tract, can be easily studied. Scheck et al. (2012) reviewed the literature pertaining to dMRI and CP in 2012. They reported decreased integrity of the descending corticospinal and ascending thalamocortical tracts, which was mainly related with ordinal classification systems like the GMFCS. However, structure-function relationships cannot be thoroughly investigated using such ordinal outcome measures. Moreover, in Scheck et al. (2012) relationships between microstructural deficits in commissural and associative pathways with motor function were conflicting. In recent years a number of studies have emerged that overcome some of these limitations of earlier work, for example by assessing continuous clinical measures and using more advanced dMRI analysis techniques. An update of the existing literature on dMRI and motor function in CP is therefore warranted. Hence, the aim of part B of this systematic review was to summarize the current literature investigating the relationship between functional outcomes and diffusion metrics of brain white matter in children with CP.

2. Methodology

This systematic review was performed following the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (Liberati et al., 2009).

2.1 Search strategy

The literature search was finalized in October 2018 extracting relevant publications from the following electronic databases: PubMed, Embase, Cochrane Central Register of Controlled trials, Cinahl and Web of Science. Time frame was set as published between 29-02-2012 and 02-10-2018 for part B.

The following keywords were used:

1. "cerebral palsy" OR "Little Disease" OR "spastic diplegia" OR "congenital diplegia" OR "spastic quadriplegia" OR "spastic hemiplegia" OR "congenital hemiplegia"
2. AND "infant" OR "newborn" OR "neonate" OR "child" OR "kid" OR "youngster" OR "toddler" OR "juvenile" OR "adolescent" OR "teen" OR "youth"
3. AND "neuroimaging" OR "brain mapping" OR "brain image" OR "magnetic resonance imaging" OR "NMR imaging" OR "MR tomography" OR "diffusion tensor" OR "Functional Brain" OR ("Brain" AND "neuroradiography") OR "Tractography"
4. AND (("Gait" OR "Upper Extremity" OR "Function" OR "Motor" OR "Mobility" OR "Manual" OR "Walking") AND ("Outcome" OR "Assessment" OR "Measure" OR "Classification" OR "Scale" OR "Ability")) OR "Motor Function" OR "functional mobility scale" OR "Gross motor function classification" OR " Bimanual Fine Motor Function" OR "Manual Ability Classification System"

2.2 Study selection

In order to avoid study bias, studies were assessed by two independent reviewers (MLP and AF) and were included according to the following criteria: full text peer-reviewed articles, in English language, published between 29.02.2012 and 02.10.2018. In case of disagreement, consensus was obtained by discussion or involvement of a third author (IF). Included study types were cross-sectional cohort studies, intervention studies reporting baseline data, case-control studies or case series. Studies were included when they involved a study population with more than 50% children (age 0-18 years) diagnosed

with CP and reported the relationship between dMRI and gross and/or fine motor function. Reviews, case reports, study protocols, conference abstracts, comments, notes or editorials were excluded as well as studies reporting functional magnetic resonance imaging or (functional) near infrared spectroscopy. Cross-reference checks of related citations were performed.

2.3 Risk of bias assessment and data extraction

Risk of bias was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies published by the National Heart, Lung and Blood Institute, which was slightly adapted according to the study designs included in this review (National Heart Lung and Blood Institute).

All data was extracted independently by the two independent reviewers (MLP and AF). A third person (LM) checked both data sheets for discrepancies. For all studies, the following data was extracted and summarized: population data, methodology used (region of interest (ROI) analysis, tractography, whole brain connectivity approach), imaging characteristics (i.a. b-value, number of directions), region or tracts of interest, diffusion metrics (fractional anisotropy, mean/axial/radial diffusivity, asymmetry indices) and clinical outcome measures.

3. Results

3.1 Study selection

After a first search, 3993 records were identified through electronic databases and screened by two independent reviewers. The titles and abstracts of these records were screened for their eligibility, resulting in a first selection of 373 papers. The full manuscript of these papers was further assessed. Studies were excluded if they were published in languages other than English (n=2), did not meet the inclusion criteria (n=24), concerned a study population that did not primarily consist of children with CP (n=73), did not report neuroimaging and/or motor function (n=122) or the reported neuroimaging and functional outcome were not related (n=88). This resulted in a remaining number of 64 studies.

The 64 included studies were further subdivided according to the type of neuroimaging used: 58 studies used sMRI, of which 13 studies additionally acquired diffusion weighted imaging to study regions or white matter tracts of interest in relation to functional outcomes. Six studies only reported dMRI (See **Figure 1**). In this part of the review, a total of 19 studies were included. Based on the risk of bias assessment, studies were rated as fair to good (see Appendix A).

3.2 Participants and study characteristics

In total, 577 children with CP were included in this review, of which the majority were diagnosed with spastic, unilateral CP (uCP) (N=481). The remaining 69 children had spastic, bilateral CP (bCP). The number of participants ranged from 10 to 50 (median 31; mode 36). The age of participants ranged between 0 and 22 years with mean age ranging from 5.6 months to 15 years. Sixteen studies investigated the relation between white matter integrity and upper limb function in children with uCP. Most studies evaluated bimanual performance (i.e. Assisting Hand Assessment, bimanual tasks) and/or unimanual capacity (i.e. Jebsen Taylor Hand Function Test, Melbourne Assessment of Unilateral Upper

Limb Function, Box and Blocks test, KINARM, Chedoke-McMaster Stroke Assessment, perdue pegboard, Pediatric Arm Function Test, functional level of hemiplegia scale). Some studies additionally included participation outcomes (i.e. Assessment of Motor and Process Skills motor component, The Canadian Occupational Performance Measure performance score) or a parent-reported questionnaire (i.e. Children's Hand-use Experience Questionnaire, Pediatric Motor Activity Log-Revised, ABILHAND-kids questionnaire) or measures of somatosensory function (i.e. stereognosis, two-point discrimination, position sense, graphesthesia) or mirror movements. In bilateral CP, two studies reported the relation with the GMFCS and the MACS (Arrigoni et al., 2016; Wang, Fan, Xu, & Wang, 2014). One study included measures of muscle strength and spasticity of the upper and lower limb in a sample including children with uCP and bCP (Meyns et al., 2016). Table 1 displays the patient characteristics and functional outcomes of each study. In Appendix B, a detailed description of the included outcome measures can be found.

Regarding the MRI acquisition of the diffusion weighted images, b-values and number of directions differed across the studies. Most frequently, a b-value of 1000 or lower was used with 6 to 45 directions (Arrigoni et al., 2016; Gupta et al., 2017; Hodge, Goodyear, Carlson, Wei, & Kirton, 2017; Kim, Kwon, & Son, 2015; Kim & Son, 2015; Kuczynski, Carlson, et al., 2017; Kuczynski, Dukelow, et al., 2018; Mackey, Stinear, Stott, & Byblow, 2014; Meyns et al., 2016; Rickards et al., 2014; Wang et al., 2014; Weinstein et al., 2014, 2015, 2018). These studies mainly used region of interest (ROI) analyses or DTI tractography to assess specific white matter tracts of interest, except for one study which applied a whole brain connectivity approach. One research group in Australia used a b-value of 3000 with 64 directions, which allowed them to use higher order models to analyze the data, such as constrained spherical deconvolution (CSD) (Fiori et al., 2015; Pannek, Boyd, Fiori, Guzzetta, & Rose, 2014; Reid, Cunnington, Boyd, & Rose, 2016; Tsao, Pannek, Boyd, & Rose, 2015; Tsao, Pannek, Fiori, Boyd, & Rose, 2014). The reported DTI metrics included fractional anisotropy, mean diffusivity, radial and axial diffusivity, streamline count and/or asymmetry indices, which varied between the studies. Study characteristics are displayed in Table 2. In Appendix C, a detailed overview of the parameters of the imaging analysis is provided.

Table 1. Participant characteristics and functional outcomes.

Article	N (TDC)	N (CP)	CP subtype		Sex (M/F)	Mean age	Age range	Functional outcome measures
			uCP	bCP				
Arrigoni et al. 2016	25	25	0	25	16/9	11.8y ± 3.1y	7.7-16.8y	GMFCS, MACS
Fiori et al. 2015	18	36	36	0	20/16	12.61y ± 3.2y	NP	AHA, JTHFT, MUUL
Gupta et al. 2017	NA	24	24	0	13/11	10.5y ± 3.3y	7-18y	stereognosis, TPD, AHA, JTHFT, B&B
Hodge et al. 2017	NA	28	28	0	18/10	10.3y ± 4.6y	6-18y	AHA, MA2, PSOM
Kim et al. 2015a	NA	36	36	0	26/10	5.6m ± 3.2m	0-12m	functional level of hemiplegia scale
Kim et al. 2015b	40	40	40	0	28/12	13.7m ± 3.0m	10-20m	functional level of hemiplegia scale
Kuczynski et al. 2017	21	29	29	0	18/11	12.05y ± 3.5y	6-19y	position sense, stereognosis, graphesthesia, AHA, MUUL, KINARM
Kuczynski et al. 2018	26	33	33	0	22/11	11.9y ± 3.95y	6-19y	MM, AHA, MUUL, CMSA, perdue pegboard, KINARM
Mackey et al. 2014	NA	20	20	0	11/9	15y ± 3y	12-22y	MUUL, B&B, bimanual tasks, ABILHAND-kids
Meyns et al. 2016	NA	50	25	25	32/18	6.3y ± 2.1y	3-12y	muscle spasticity and strength
Pannek et al. 2014	17	50	50	0	26/24	10.95y ± 3.15y	5-17y	AHA
Reid et al. 2016	NA	31	31	0	14/17	11.8y ± 2.9y	NP	AHA, JTHFT, MUUL, AMPS-M, COPM-P
Rickards et al. 2014	NA	10	10	0	7/3	3.2y ± 1.7y	2.7-7.6y	PAFT, PMAL-R
Tsao et al. 2014	15	40	40	0	21/19	11.5y ± 3.1y	5-16y	stereognosis, TPD, AHA, JTHFT, MUUL
Tsao et al. 2015	15	42	42	0	21/21	11.3y ± 3.3y	5-16y	stereognosis, TPD, AHA, JTHFT, MUUL
Wang et al. 2014	40	46	0	46	30/16	22.4m ± 6.7m	3-48m	GMFCS
Weinstein et al. 2014	14	14	14	0	8/6	10.6y ± 2.7y	7-14y	MM, AHA, JTHFT, CHEQ
Weinstein et al. 2015	NA	12	12	0	6/6	11y ± 3.6y	7-16y	AHA, JTHFT
Weinstein et al. 2018	NA	11	11	0	7/4	10.1y ± 2.7y	7-16y	JTHFT

uCP, unilateral cerebral palsy; bCP, bilateral CP; NA, not applicable; NP, not provided; GMFCS, Gross Motor Functional Classification System; MACS, Manual Ability Classification System; AHA, Assisting Hand Assessment; JTHFT, Jebsen-Taylor Hand Function Test; MUUL, Melbourne Assessment of Unilateral Upper Limb Function; TPD, two-point discrimination; B&B, box and blocks test; MA2, Melbourne Assessment 2; PSOM, Pediatric Stroke Outcome Measure; MM, mirror movements; CMSA, Chedoke-McMaster Stroke Assessment; AMPS-M, Assessment of Motor and Process Skills motor component; COPM-P, Canadian Occupational Performance Measure performance score; PAFT, Pediatric Arm Function Test; PMAL-R, Pediatric Motor Activity Log - Revised; CHEQ, Children's Hand-use Experience questionnaire.

Table 2: Study characteristics

Article	dMRI acquistion & reconstruction approach				Analysis technique			Anatomical region or tract of interest	Diffusion metrics
	b-value	# directions	dMRI model	probabilistic/ deterministic (algorithm)	ROI	FT-3D VOI	Whole brain		
Arrigoni et al. 2016	300 &1100	15 & 53	DTI	N/A	X		X	Whole brain (VBA) & WM atlas ROIs	FA, MD, RD and AD
Fiori et al. 2015	3000	64	CSD	prob (CSD)		X		corticopontocerebellar tract	asymmetry index SC
Gupta et al. 2017	800	55 / 65	DTI	deter (Runge-Kutta)		X		CST, ML	tract present/ absent
Hodge et al. 2017	1000	6	DTI	deter (FACT)	X	X		cerebral peduncle, CST	FA, MD, RD and AD and asymmetry indices
Kim et al. 2015a	1000	32	DTI	deter (FACT		X		CST	SC, FA, MD
Kim et al. 2015b	1000	32	DTI	deter (FACT)		X		CST	SC, FA, MD
Kuczynski et al. 2017	750	32	DTI	prob (n.s.)		X		ML	SC, FA, MD, RD and AD; degree of overlap
Kuczynski et al. 2018	750	32	DTI	prob (n.s.)		X		CST	FA, MD, RD and AD
Mackey et al. 2014	1000	25	DTI	N/A	X			PLIC	FA, asymmetry index FA
Meyns et al. 2016	800	45	DTI	deter (Basser)		X		CST	FA, MD and asymmetry indices
Pannek et al. 2014	3000	64	CSD	prob (CSD)			X	whole brain connectivity	FA
Reid et al. 2016	3000	64	CSD	prob (CSD)		X		thalamocortical and corticomotor tracts	asymmetry index FA and MD
Rickards et al. 2014	1000	45	DTI	prob (n.s.)		X		CST	FA
Tsao et al. 2014	3000	64	CSD	prob (CSD)		X		corticomotor tracts	asymmetry index SC; FA, MD
Tsao et al. 2015	3000	64	CSD	prob (CSD)		X		thalamocortical tracts	asymmetry index SC
Wang et al. 2014	800	15	DTI	deter (FACT)		X		SCP, MCP, CST	FA
Weinstein et al. 2014	1000	19	DTI	deter (FACT)	X	X		PLIC, CC, CST	SC, FA, MD, AD, RD
Weinstein et al. 2015	1000	19	DTI	deter (FACT)		X		CC, CST	FA, MD, AD, RD
Weinstein et al. 2018	1000	19	DTI	deter (FACT)		X		CC and CST	FA, MD, AD, RD

ROI, region of interest; CSD, constrained spherical deconvolution; deter, deterministic tractography; FACT, Fiber Assignment by Continuous Tracking; prob, probabilistic tractography; CST, corticospinal tract; ML, medial lemniscus; PLIC, posterior limb of internal capsule; ACC, anterior cingulate cortex; SCP, superior cerebellar peduncle; MCP, middle cerebellar peduncle; CC, corpus callosum; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity; SC, streamline count; AFD, apparent fiber density; n.s., not specified; N/A, not applicable; FT, fiber-tractography; VOI, volume of interest; VBA, voxel-based analysis; WM, white matter

3.3 Results according to analysis technique

3.3.1 Region of interest

Three studies used a manual ROI analysis, two targeting the PLIC (Mackey et al., 2014; Weinstein et al., 2014) and one the cerebral peduncle (Hodge et al., 2017). All three studies included children with uCP only. One other study, including children with bCP, performed a ROI analysis of 20 regions using automated ROIs from the Johns Hopkins University DTI atlas (Arrigoni et al., 2016).

In children with *uCP*, differences in DTI metrics, consistent with microstructural abnormality (i.e. lower FA and SC, higher MD) were found in the PLIC along the affected CST compared to the less affected hemisphere or the brain of typically developing children (Mackey et al., 2014; Weinstein et al., 2014). In children with *bCP*, differences in DTI metrics emerged in both motor (e.g. CSTs and thalamic radiations) and non-motor pathways (e.g. the middle and posterior parts of the corpus callosum, optic radiations, superior longitudinal fasciculi, cingulum, and cerebellar peduncles). The magnitude of these differences differed between regions, with the largest white matter abnormalities in the posterior corona radiata, thalamic radiations, corpus callosum, cingulum, and superior cerebellar peduncles (Arrigoni et al., 2016).

Moreover, in children with *uCP*, white matter microstructural impairment of the affected PLIC (Mackey et al., 2014; Weinstein et al., 2014) and cerebral peduncle (Hodge et al., 2017) was moderately to strongly associated with worse upper limb function (r=-0.49 to -0.83). In children with *bCP*, Arrigoni et al. (2016) reported less integrity in the CST's, posterior thalamic radiations, corona radiata, and superior longitudinal fasciculus in children classified in higher GMFCS (r=-0.41 to -0.69) and MACS levels (r=-0.40 to 0.54). White matter integrity of the inferior cerebellar peduncle, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and uncinated fasciculus were additionally correlated only with GMFCS levels (r=-0.40 to -0.50).

3.3.2 Tractography

Sixteen studies focused on specific white matter tracts of interest (Fiori et al., 2015; Gupta et al., 2017; Hodge et al., 2017; Kim et al., 2015; Kim & Son, 2015; Kuczynski et al., 2017; Kuczynski, Dukelow, Semrau, & Kirton, 2016; Meyns et al., 2016; Reid et al., 2016; Rickards et al., 2014; Tsao et al., 2015, 2014; Wang et al., 2014; Weinstein et al., 2014, 2018, 2015). Nine of these studies used a deterministic fiber-tracking algorithm (Gupta et al., 2017; Hodge et al., 2017; Kim et al., 2015; Kim & Son, 2015; Meyns et al., 2016; Wang et al., 2014; Weinstein et al., 2014, 2018, 2015), of which 'Fiber Assignment with Continuous Tracking' (FACT, (Hangyi Jiang, Zijl, Kim, Pearlson, & Mori, 2006)) was most frequently used. Seven studies used probabilistic tracking methods (Fiori et al., 2015; Kuczynski et al., 2017, 2016; Reid et al., 2016; Rickards et al., 2014; Tsao et al., 2015, 2014). Most studies used CSD of which one was fMRI driven (Reid et al., 2016), and two other studies performed an automated atlas based approach involving seeding streamlines randomly over the whole brain and extracting tracts based on cortical projections (Tsao et al., 2015, 2014). Of these 16 studies, only one study included children with bCP (Wang et al., 2014), and one other study included both children with uCP and bCP (Meyns et al., 2016). All other studies focused on children with uCP.

Most studies investigated one specific tract of interest, of which the corticospinal tract (CST) was most frequently investigated (Hodge et al., 2017; Kim et al., 2015; Kim & Son, 2015; Kuczynski, Dukelow, et al., 2018; Meyns et al., 2016; Rickards et al., 2014). Thalamocortical (Reid et al., 2016; Tsao et al., 2015) and corticomotor (Reid et al., 2016; Tsao et al., 2014) projections were assessed in two studies, the medial lemniscus (Kuczynski et al., 2017) and the corticopontocerebellar tracts (Fiori et al., 2015) in one study. Other studies targeted the CST along with the medial lemniscus (Gupta et al., 2017), corpus callosum (Weinstein et al., 2014, 2018, 2015) or the superior and middle cerebellar peduncles (Wang 2014).

In children with *spastic bCP,* mean FA was significantly reduced in the bilateral superior and middle cerebellar peduncles as well as in the CST's compared to the ipsilateral regions of typically developing children (Wang et al., 2014). In children with *uCP*, studies also showed decreased white matter integrity in the CST or medial lemniscus in the lesioned hemisphere compared to the dominant hemisphere of typically developing children (Kuczynski, Carlson, et al., 2017; Kuczynski, Dukelow, et al., 2018). Other studies in uCP further showed white matter microstructural impairment in the CST, projections traversing the PLIC as well as thalamocortical projections, the medial lemniscus, the corpus callosum and the corticopontocerebellar tracts of the lesioned hemisphere compared to the less affected hemisphere or typically developing children (Fiori et al., 2015; Hodge et al., 2017; Kim et al., 2015; Kim & Son, 2015; Kuczynski, Carlson, et al., 2017; Kuczynski, Dukelow, et al., 2018; Tsao et al., 2015, 2014, Weinstein et al., 2014, 2018). Interestingly, Kim et al. (2015b) found a higher SC, but lower FA in the less affected CST of children with uCP compared to the dominant hemisphere of typically developing children. Kuczynski et al. (2018) reported that children with uCP with an arterial ischaemic stroke have lower FA values in the CST of the less affected hemisphere compared to children with a periventricular venous infarction and typically developing children.

In children with *bCP*, Wang et al. (2014) reported significant, though low, correlations between mean FA of both CST's, superior and middle cerebellar peduncles and GMFCS level, indicating less microstructural abnormality in children with better gross motor abilities. Meyns et al. (2016) further reported a moderate, positive correlation between asymmetry in muscle spasticity and strength of the lower limbs (r=0.61) and asymmetry between the CST"s (r=0.64).
In children with *uCP*, decreased upper limb function of the impaired hand has been associated with reduced white matter microstructural impairment in a number of tracts, including the affected CST (Gupta et al., 2017; Hodge et al., 2017; Kuczynski, Dukelow, et al., 2018; Rickards et al., 2014; Weinstein et al., 2014, 2015), the less affected CST (Kim & Son, 2015; Weinstein et al., 2014, 2015), corticomotor (Reid et al., 2016; Tsao et al., 2014) and thalamocortical projections (Reid et al., 2016; Tsao et al., 2015), the medial lemniscus (Gupta et al., 2017; Kuczynski et al., 2017), the corpus callosum (Weinstein et al., 2014, 2018, 2015) and the corticopontocerebellar tracts (Fiori et al., 2015). Gupta et al. (2017) investigated both the CST and medial lemniscus and concluded that both tracts influence hand function in children with uCP. Although, the relative contribution was larger for the medial lemniscus as compared to the CST as shown by larger effect sizes (d=0.92-2.34 and d=0.48-1.21,

respectively). Weinstein et al. (2014, 2018) additionally found that white matter integrity of the corpus callosum was highly related with movement speed of the dominant hand and mirror movements (r=-0.71-0.86). Finally, Meyns et al. (2016) found a strong, negative correlation between lower limb strength and white matter integrity of the affected CST (r=-0.80). Also the asymmetry in spasticity was negatively associated with asymmetry between both CST's (r=-0.63).

3.3.3 Whole brain

Arrigoni et al. (2016) performed a whole brain voxel-based analysis of the DTI scalar maps in children with spastic bCP. Pannek et al. (2014) performed a connectivity network analysis based on whole brain CSD tractography in children with uCP caused by periventricular white matter lesions. Both studies reported reduced white matter integrity in a number of connections, including but not limited to regions directly associated with the sensorimotor system as compared to typically developing children.

Arrigoni et al. (2016) did not correlate the voxel-based DTI results with functional outcome measures. However, Pannek et al. (2014) revealed that the CST, thalamocortical projections and fronto-parietal association pathways showed reduced integrity in children with *uCP* compared to typically developing children, which was low to moderately correlated with bimanual performance (r^2=0.22-0.44).

4. Discussion

In this study, we reviewed the existing literature on the relationship between brain lesion type and motor outcome (part A) as well as between white matter abnormalities and sensorimotor function in children with CP (part B). While part A provides a more general overview of the level of gross motor functioning and manual ability dependent on lesion type, part B describes more specific relationships between white matter abnormalities across the whole brain and measures of sensorimotor function. This manuscript handles part B of the review, for which nineteen studies were retained from the systematic search, including a total of 577 children with CP. The results indicated that white matter integrity is decreased across the sensorimotor association areas, but also in non-motor tracts in children with uCP and bCP compared to typically developing children. The majority of the studies focused on children with uCP, and revealed that more pronounced white matter abnormalities are associated with a worse function of the upper limb. No clear conclusions can be made on bCP as this was only investigated in three studies. There were no studies on dyskinetic CP.

White matter integrity of affected tracts

In the review by Scheck et al. (2012), it was concluded that significant damage to both descending motor and ascending sensorimotor tracts contribute to the neuropathogenesis of CP. This is further confirmed by the results of this update. Our review further added to the literature that in children with spastic uCP and bCP, white matter integrity loss is widespread across the whole brain and not solely restricted to sensorimotor connections in comparison to typically developing children (Arrigoni et al., 2016; Pannek et al., 2014). Moreover, one study found that white matter integrity of the corpus callosum was decreased in children with uCP compared to typically developing children (Weinstein et al., 2014), which was most prominent at the midbody. Finally, two included studies targeted the pontocerebellar fibers reporting a

decreased integrity in children with uCP and bCP compared to typically developing children (Fiori et al., 2015; Wang et al., 2014). Such widespread brain damage in children with CP is not surprising taking into account the developmental processes the brain undergoes at the time-point of damage. The most significant developmental changes occur between the second half of gestation and the first three months postnatally (Hadders-Algra, 2018), a time window wherein the lesion originates in children with CP. Moreover, the presence of Wallerian degeneration and/or the lack of generating white matter fibers due to the presence of grey matter lesions, further contributes to the widespread white matter abnormalities in children with CP.

Relationship between white matter integrity and motor function

Scheck et al. (2012) concluded that the relationship between white matter integrity and motor function could not be well-established as only few studies used continuous outcome measures. However, studies using such outcome measures have emerged in the last years, and in particular in children with uCP. While in part A of this review (Franki et al. 2019), it was concluded that insufficient information was extracted to reliably relate manual motor function (i.e. MACS) with sMRI results, the results of this review showed clear relationships between upper limb function and white matter integrity of the descending CST and ascending thalamocortical tracts in children with uCP, which has also been recently confirmed by a meta-analysis (Jiang et al., 2019). However, overall low to moderate correlations were found, indicating that the existing variability in upper limb function in children with uCP cannot be explained based solely on one white matter tract. Interestingly, the meta-analysis reported that FA in the PLIC was more strongly related with upper limb motor function compared to FA in the full fiber tracts. Nevertheless, to date only Gupta et al. (2017) compared the significant contribution of the CST along with the medial lemniscus to upper limb function variability. These authors reported a stronger contribution of the somatosensory tract (i.e. medial lemniscus) as compared to the CST. Unfortunately, this study did not use diffusion metrics as outcome parameters. Instead, the outcome of the tractography was binarized in ‘present’ or ‘absent’, which does not take into account the severity of the white matter damage. Yet the severity of the damage is a crucial factor when explaining the variability in function, in particular for the CST, as all children with CP are expected to have a damaged CST (Dinomais et al., 2015). Moreover, fine motor control is a complex process involving several brain areas, and not only the CST and somatosensory tracts.

Strikingly, the relation between white matter integrity of the corpus callosum and function is still not well studied, despite its essence in, for example, bimanual coordination (Gooijers & Swinnen, 2014). Most bimanual activities require a differential role for each hand, i.e. one hand manipulates while the other hand fixates an object. During manipulation of an object, the corpus callosum allows interhemispheric communication, facilitating information transfer on the position of both hands with respect to each other, as well as preventing the occurrence of mirror movements through interhemispheric inhibition. So far, only one research group investigated the relationship with upper limb function and reported decreased with matter integrity of the genu, midbody and splenium of the corpus callosum in children with lower levels of bimanual performance and unimanual dexterity (Weinstein et al., 2014, 2018, 2015). They

additionally revealed a reduced amount of SCs in the midbody (Weinstein et al., 2014), but increased FA across the whole corpus callosum (Weinstein et al., 2018) in children with uCP showing mirror movements. Mackey et al. (2014) further found a decreased interhemispheric inhibition, assessed with transcranial magnetic stimulation, in adolescents and young adults with uCP with a less dexterous use of the impaired upper limb. Unfortunately, mirror movements were not assessed in this study. Moreover, the studies by Weinstein et al. (2014, 2015, 2018) tracked the fibers of the corpus callosum using a geometric distribution scheme, while it would be interesting to specifically target the sensorimotor transcallosal fibers. Together, further research is required to unravel the role of the corpus callosum in explaining motor deficits in children with CP.

White matter integrity of the pontocerebellar fibers also appeared to correlate with bimanual performance (Fiori et al., 2015) in uCP as well as with gross motor function in bCP (Wang et al., 2014), though correlations were low. While the cerebellum is not involved in the direct execution of the movement, it plays a critical role in fine-tuning movements regarding coordination, accuracy and smoothness on an unconscious level (Gilman, Bloedel, & Lechtenberg, 1981). As such the cerebellum has been shown to be a key structure in complex bimanual movements (Swinnen & Wenderoth, 2004). Nevertheless, white matter integrity of the cerebellum and its relationship with motor function needs further exploration in children with CP.

Studies examining structure-function relationships in children with bCP were limited (Arrigoni et al., 2016; Meyns et al., 2016; Wang et al., 2014). Moreover, mainly global classification scales (i.e. GMFCS, MACS) were related with DTI metrics in this study group. Also part A of this review reported an equal distribution across the GMFCS levels independent of the type of the lesion (Franki et al. 2019). Meyns et al. (2016) additionally showed a relationship between white matter abnormalities of the CST and muscle weakness and spasticity of the lower limbs. Unfortunately, no studies in children with dyskinetic CP met the eligibility criteria for inclusion in this part of the review. However, one recent study investigated whole brain connectivity in dyskinetic CP and investigated the relation with GMFCS and MACS (Ballester-Plané et al., 2017). This study was not retained from the systematic search as more than half of the participants were adults. Nevertheless, the results of this study reported a relationship between the integrity of a large bilateral network, comprising mainly basal ganglia and thalamic connections with primary sensorimotor areas, frontal and parietal areas, and GMFCS and MACS levels. Interestingly, these authors found, similarly to Arrigoni et al. (2016) in bCP, that GMFCS levels, but not the MACS, were related with the integrity of non-motor connections. This may indicate that the GMFCS better captures the overall morbidity of children with bilateral and dyskinetic CP, including hearing, visual and communicative difficulties compared to the MACS.

Relationship between white matter integrity and sensory function

Despite the known essence of intact sensory function for adequate motor function, the relation between white matter integrity of the sensorimotor tracts and sensory function was not systematically assessed. Only four of the 19 studies included measures of sensory function, all showing associations with white

matter microstructural impairment of the sensorimotor tracts (Gupta et al., 2017; Kuczynski et al., 2016; Tsao et al., 2015, 2014). Interestingly, Kuczynski et al. (2017) could not find a relationship between white matter integrity of the medial lemniscus and clinical measures of sensory function. However, position sense, quantified with the use of robotics correlated moderately with white matter integrity of the medial lemniscus.

In sum, advancements have been made since the review by Scheck et al. (2012). The studies included in the current review generally focused on one subtype of CP. This aids in the interpretation of the results, as the findings will be specific for that subgroup and not determined by extremes (e.g. dyskinetic CP, which are most often classified in the highest levels of the GMFCS and MACS (Gorter et al., 2004)). Moreover, in addition to the homogeneity of the study groups, the study sample sizes are relatively larger as well, with only five of the 19 included studies having less than 20 participants enrolled. Finally, the majority of the studies used standardized continuous outcomes measures, all assessing the function of the upper limb.

Limitations

Some critical reflections on this review are warranted. First, large methodological differences were present between the studies regarding the neuroimaging methodologies as well as regarding functional outcome measures and the age of the included participants. Moreover, more than half of the studies used a deterministic approach to generate the fiber bundles of interest. However, deterministic approaches are known to be less accurate in areas of crossing fibers, underestimating the amount of anisotropy (Jones, 2010; Pierpaoli et al., 2001). Higher order models, such as CSD can provide a more accurate estimate of fiber bundle organization in white matter networks. Only five studies used CSD to assess white matter integrity, which were all published by the same research group and their collaborators. Secondly, seven studies reported SC as an outcome measure, of which four studies referred to ‘number of fibers’. However, the amount of generated streamlines is not a direct measure of the amount of fibers (Jones, Knösche &Turner, 2013). Moreover, SC is an unstable metric and may be modulated by the length or curvature of the pathway, as well as by local variations in signal to noise ratio. Subsequently, interpreting this metric as fiber density would be incorrect nor can it be compared between participants (Jones, Knösche &Turner, 2013). Future studies that incorporate SC as an outcome measure should take this into account. Finally, large population based studies are lacking, though study samples are in general larger than those reported in Scheck et al. (2012). Moreover, the majority of children had periventricular white matter lesions, i.e. 65%. This percentage is higher than reported in existing literature, which is usually around 50% (Feys et al., 2010; Krägeloh-Mann & Horber, 2007), indicating an overrepresentation of children with predominantly white matter lesions. A possible explanation is that in children with cortical and deep grey matter lesions, lesions are more severe (Mailleux et al., 2017) impacting the structural anatomy of the brain. A changed structural anatomy confounds manual ROI placement and obstructs automated analysis approaches. Hence, this may indicate that children with cortical and deep grey matter lesions, and in particular with severe lesions, may be underrepresented in current dMRI literature.

Future directions

The confirmatory results of this review after Scheck et al. (2012) underline the significance of using dMRI in unravelling structure-function relationships in children with CP. Still future research is needed to further improve our insights into this complex relationship. So far, most studies investigated the relationship between motor function and white matter integrity in a single tract based on a predefined hypothesis. However, one could expect that the predictive value of function would increase when knowledge about multiple white matter tracts is combined. So far, this has not been done. Examining the combined predictive value of multiple white matter tracts would aid in obtaining more insights on the neuropathogenesis of functional deficits in children with CP. Moreover, including other brain lesion characteristics known to relate significantly with function such as the corticospinal tract wiring pattern (Simon-Martinez et al., 2018), might further strengthen the predictive model. Also, large study samples would be required to study how multiple brain lesion characteristics contribute to the variation in motor function.

Secondly, besides dMRI, also functional MRI may aid in further unravelling structure-function relationships in children with CP by visualizing functional connectivity (Saunders, Carlson, Cortese, Goodyear, & Kirton, 2019; Simon-Martinez et al., 2019; Woodward et al., 2019). Recently, the use of functional connectivity has even shown prognostic potential with respect to early detection of motor impairments in neonates (Linke et al., 2018). Although these promising results points towards an optimization of early and accurate prediction of motor outcome, further studies are needed to establish the added value of using functional MRI in the clinical setting. Moreover, while dMRI evaluates structural connectivity and may identify damaged or reorganized structural networks, functional MRI reflects whether information transfer still persists or not in such networks. So far, only Lee et al. (Lee et al., 2017) assessed both structural and functional connectivity across the whole brain in children with bCP. These authors revealed that structural connectivity networks across the whole brain were severely impaired, while the information transfer (i.e. functional connectivity) remained relatively spared compared to typically developing children. Interestingly, they further found that in the motor network functional connectivity was more severely damaged compared to the structural connectivity network. Unfortunately, Lee et al. (2017) did not investigate the relationship between the structural-functional connectivity imbalance and functional outcomes. Nevertheless, future research focusing on functional connectivity will undoubtedly contribute to a better understanding of the complex neural mechanisms underlying CP. Thirdly, recent studies suggest that the function of the dominant hand of children with uCP does not equal that of typically developing peers (Basu et al., 2017; Rich, Menk, Rudser, Timothy, & Gillick, 2017). Two studies indeed reported white matter abnormalities of the less affected CST compared to typically developing children (Kim & Son, 2015; Kuczynski et al., 2018). Moreover, Kuczynski et al. (2017) reported a relationship between kinematic reaching performance of the dominant hand and diffusion parameters of the less affected CST. Also Weinstein et al. (2014) reported a relationship between white matter abnormalities of the corpus callosum and dominant hand performance. This calls for in-depth analysis of the widespread damage in the brain and how this contributes to their level of functioning. The use of more sensitive measures of function, such as robotics,

might aid in detecting more subtle changes in function and as such allow for a better discrimination between the children.

Finally, despite the fact that the relationship between white matter integrity and upper limb function is well investigated, the lower limb as well as the trunk remains understudied. The greater interest in upper limb structural-function relationships, particularly in children with uCP, may be explained by significance of the upper limb and hand in daily life. As the majority of children with uCP become ambulant (i.e. GMFCS level1 or 2), their level of self-care independence will be largely determined by the severity of the upper limb deficits (Russo et al., 2019). Subsequently, there is a major interest in unravelling the underlying neural mechanisms of upper limb dysfunction in children with uCP. Although we still do not have all answers and this topic remains highly relevant to study, future research should also focus on exploring the relation between white matter integrity and the function of the lower limbs and trunk.

Conclusion

White matter integrity is decreased in sensorimotor connections across the brain, but also in non-motor areas in children with uCP and bCP. Results on structure-function relationships in children with bCP were, however, limited, and absent in dyskinetic CP. Nevertheless, in children with uCP the severity of the white matter damage of specific sensorimotor tracts appears to be clearly related with bimanual performance and unimanual capacity. The exact contribution of the descending motor versus ascending somatosensory tracts on upper limb function still remains elusive. Also the role of the corpus callosum, as well as associative pathways warrants further investigation. Moreover, correlations were mainly low to moderate, indicating that one single tract cannot explain the whole variability in motor function in children with CP. This underlines the need to study a predictive model including multiple white matter tracts of interest.

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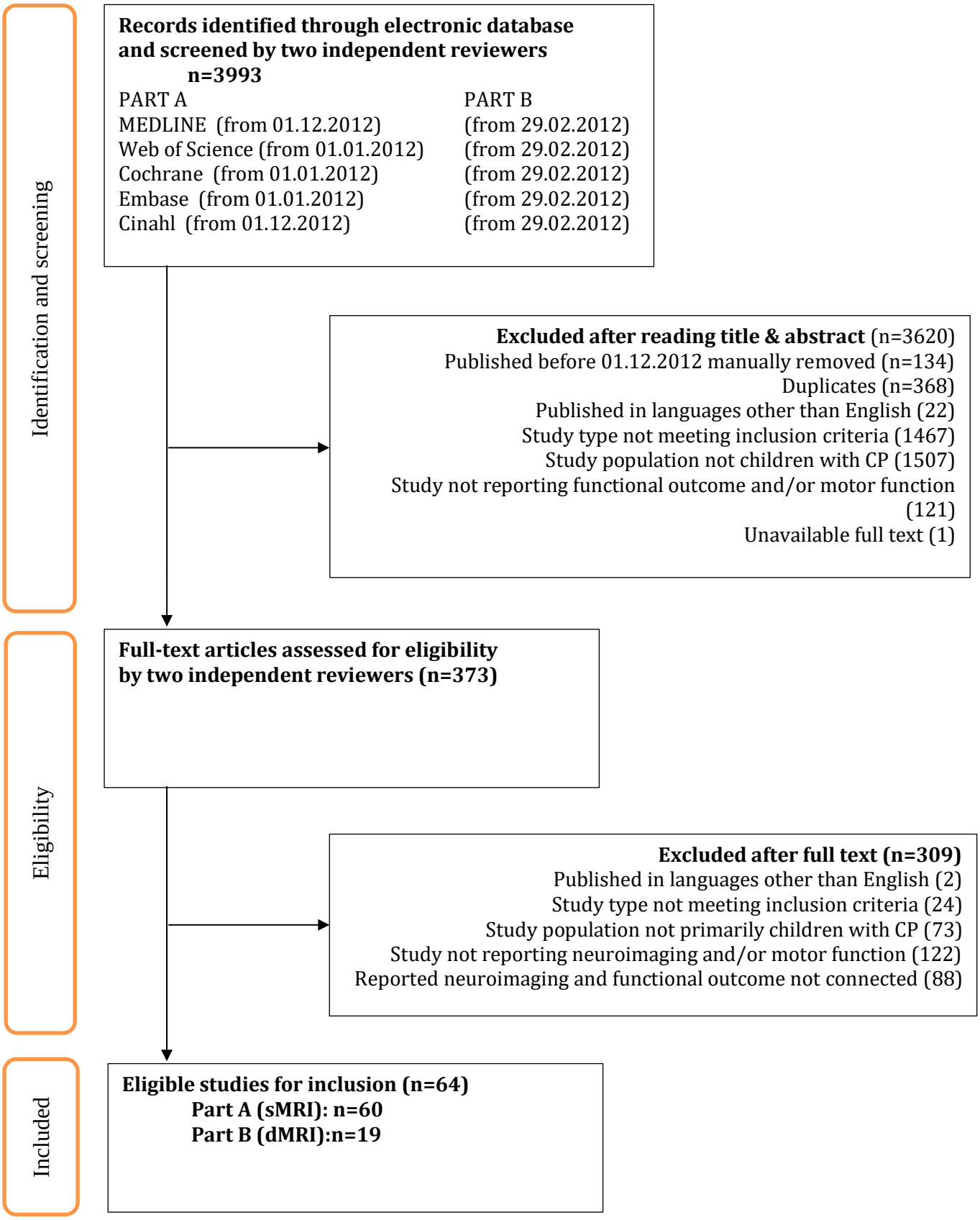
Figure 1. Flow-chart



Appendix A.1: Risk of bias assessment - Criteria
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, the time gap between the MRI scan and motor assessment was not more than 1 month?*
7. Were the diffusion parameters clearly defined, valid, and reliable?*
8. Were the outcome measures of motor function clearly defined, valid, reliable, and implemented consistently across all study participants?*
9. Were the assessors of the DTI analysis blinded to the motor function of participants?*
10. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between DTI and motor outcome?*
*These criteria were adapted from the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies published by the National Heart, Lung and Blood Institute. Items that were adapted for the purpose of this systematic review are marked with *. Four items were left out (criteria 7, 8, 10, 13 of the original version) as these items were not applicable for the designs of the included studies.*

Appendix A.2: Risk of bias assessment - Results

Criteria	1	2	3	4	5	6	7	8	9	10	
Arrigoni et al. 2016	1	1	NR	1	0	NR	1	1	NR	0	50%
Fiori et al. 2015	1	1	1	1	0	1	1	1	NR	0	70%
Gupta et al. 2017	1	1	NR	1	1	NR	1	1	1	0	70%
Hodge et al. 2017	1	1	1	1	0	NR	1	1	1	1	80%
Kim et al. 2015a	1	1	0	1	0	1	1	1	NR	0	60%
Kim et al. 2015b	1	1	1	1	0	1	1	1	NR	0	70%
Kuczynski et al. 2017	1	1	1	1	0	NR	1	1	1	1	80%
Kuczynski et al. 2018	1	1	1	1	0	NR	1	1	NR	1	70%
Mackey et al. 2014	1	1	NR	1	0	NR	1	1	NR	0	50%
Meyns et al. 2016	1	1	1	1	0	CD	1	1	0	1	70%
Pannek et al. 2014	1	1	1	1	0	1	1	1	NR	0	70%
Reid et al. 2016	1	1	0	1	0	1	1	1	1	1	80%
Rickards et al. 2014	1	1	NR	1	1	1	1	1	NR	0	70%
Tsao et al. 2014	1	1	1	1	0	NR	1	1	NR	1	70%
Tsao et al. 2015	1	1	1	1	0	NR	1	1	NR	0	60%
Wang et al. 2014	1	1	NR	1	0	1	1	1	1	0	70%
Weinstein et al. 2014	1	1	NR	1	0	1	1	1	1	1	80%
Weinstein et al. 2015	1	1	1	1	0	1	1	1	NR	0	70%
Weinstein et al. 2018	1	1	1	1	0	NR	1	1	NR	0	60%

NR, not reported; CD, cannot determine.

Appendix B: description of the included tests of sensorimotor function

	Test description	Reference(s)
Body structure and function		
Stereognosis	Tactical identification of familiar objects	[3], [7], [14], [15]
Two-point discrimination	Discrimination of one versus two points at the finger	[3], [14], [15]
Position sense	Identification of the end position of the thumb and wrist	[7]
Graphestesia	Identification of '3', '5' or '7' in the palm	[7]
Mirror movements	Subjective observation of mirror activity of the non-moving hand during the execution of simple tasks with the other hand	[8], [17]
Muscle spasticity	Severity of muscle spasticity in the bilateral hip flexors/extensors, knee flexors/adductors, and ankle dorsiflexors/plantarflexors by means of the modified Ashworth	[10]
Muscle strength	Muscle strength of the bilateral hip flexors/extensors, knee flexors/extensors, and ankle dorsiflexors/plantarflexors by means of the Manual Muscle Testing scale	[10]
Activity level		
Gross Motor Function Classification System (GMFCS)	The GMFCS classifies children with cerebral palsy on five different levels based on their self-initiated movement, with emphasis on sitting, transfers, and mobility ('1' = full ambulation to '5' = transportation in a manual wheelchair)	[1], [16]
Manual Ability Classification System (MACS)	The MACS classifies children with cerebral palsy on five different levels based on their self-initiated ability to manipulate objects in daily life and their need for assistance or adaptation ('1' = handles objects with ease to '5' = does not handle objects)	[1]
Functional level of hemiplegia scale	Or the *House Functional Classification*; which describes upper limb function in children with cerebral palsy on nine different levels ('0' = no use to '8' = uses the hand with complete independence)	[5], [6]
Assisting Hand Assessment	A standardized video-based observation of the spontaneous use of the impaired hand during bimanual tasks in a semi-structured play session	[2], [3], [4], [7], [8], [11], [12], [14], [15], [17], [18]
Bimanual tasks	Spontaneous use and amount of assistance of the impaired hand during five bimanual daily tasks were video-scored, using a four-point scale with a maximum score of 30	[9]
Melbourne Assessment of Unilateral Upper Limb Function (MUUL)	Comprises 16 unimanual activities to assess movement quality of the upper limb including reaching, grasping, manipulating and functional tasks resulting in one total score ('0' to '100')	[2], [7], [8], [9], [12], [14], [15]
Melbourne Assessment - 2	Revised version of the MUUL, resulting in four subscores (range of motion, dexterity, fluency and accuracy) instead of one total score	[4]
Jebsen-Taylor Hand Function Test	Assessment of movement speed during six functional tasks	[2], [3], [12], [14], [15], [17], [18], [19]
Box and Blocks Test	Number of blocks which can be transferred from one box to the other in 60 seconds	[3], [9]
Pediatric Stroke Outcome Measure – motor outcomes	This scale assesses neurological impairment of motor, cognition and language	[4]

KINARM	Robotic quantification of proprioception [7] and visually guided reaching [8]	[7], [8]
Chedoke-McMaster Stroke Assessment	Assessment of unilateral upper limb function of both hands through seven stages of movement while performing 19 tasks ('0' = paralysis to '7' = normal movement)	[8]
Perdue pegboard	Unimanual dexterity of both hands while transferring pegs in 30 seconds	[8]
Pediatric Arm Function Test	Consists of 17 unilateral and 9 bilateral tasks. Children may choose which hand they use resulting in a limb preference score	[13]
ABILHAND-kids questionnaire	Perceived difficulty of performing daily manual actions	[9]
Children's Hand-use Experience Questionnaire Pediatric Motor Activity Log-Revised	This questionnaire evaluates the experience of using the impaired hand during bimanual activities Evaluates 'how well' and 'how often' the child uses their more impaired upper limb during 22 frequently performed activities of daily life by means of a structured interview	[17] [13]
Participation level		
Assessment of Motor and Process Skills -motor component	An observational assessment of 16 motor skills and its effect on the ability to perform activities of daily living	[12]
The Canadian Occupational Performance Measure - performance score	A semi-structured interview designed to capture self-reported satisfaction with respect to their ability to carry out activities of daily life	[12]

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Appendix C: Details of tractography parameters of the studies included in the systematic review					
Article	**FA threshold**	**Curvature /angle threshold**	**Manual vs Automated**	**Region/tract of interest**	**Regions of interest / tract selection method**
Arrigoni et al. 2016	n.s.	n.s.	Automated	Whole brain (VBA) & WM atlas ROIs	Whole brain connectivity approach (20 ROI's representing the most important WM tracts included in the John Hopkins University WM tractography atlas)
Fiori et al. 2015	n.s.	n.s.	Manual	Corticopontocerebellar tract	Two-ROI approach: the seed ROI was placed on the middle cerebellar peduncles on the coronal plane of the color-coded TDI. For both right and left sides, ROI 2 was drawn on the posterior limb of internal capsule on the axial plane.
Gupta et al. 2017	n.s.	n.s.	Manual	CST, ML	Seed ROI was placed on an axial slice of the pons. No further specifications on ROI drawing are provided.
Hodge et al. 2017	0.2	50°	Manual	Cerebral peduncle, CST	Two-ROI approach: the seed ROI was drawn in the cerebral peduncle on the axial slice at the level of the decussation of the superior cerebellar peduncle. ROI 2 was placed in the posterior limb of the internal capsule.
Kim et al. 2015a	0.2	45°	Manual	CST	Two-ROI approach: A seed ROI was drawn in the anterior mid-pons, and ROI 2 was drawn in the anterior low-pons.
Kim et al. 2015b	0.2	45°	Manual	CST	Two-ROI approach: A seed ROI was drawn in the anterior mid-pons, and ROI 2 was drawn in the anterior low-pons.
Kuczynski et al. 2017	0.2	70°	Manual	ML	Two-ROI approach: the medial lemniscus and ventral posterior lateral nucleus of the thalamus.
Kuczynski et al. 2018	0.2	70°	Manual	CST	Two-ROI approach: ROI 1 was placed on the cerebral peduncle and ROI 2 in the posterior limb of the internal capsule.
Mackey et al. 2014	n.s.	n.s.	Manual	PLIC	One ROI was drawn in the posterior limb of the internal capsule.
Meyns et al. 2016	0.2	30°	Manual	CST	Two-ROI approach: A seed ROI was drawn in the cerebral peduncle and ROI 2 in the primary motor cortex.
Pannek et al. 2014	n.s.	n.s.	Automated	Whole brain connectivity	Whole brain connectivity approach to identify pathways with an altered microstructure.
Reid et al. 2016	0.1	n.s.	Manual	Thalamocortical and corticomotor tracts	Two-ROI approach: streamlines were seeded from the thalamus (thalamocortical tracts) or PLIC (corticomotor tracts) and ROI 2 was drawn on the brainstem on the first axial slice inferior to the pons.
Rickards et al. 2014	0.15	n.s.	Manual	CST	Multiple ROI approach: A seed ROI encompassed the posterior limb of the internal capsule, ROI 2 was placed in the cerebral peduncles, and ROI 3 at the junction of brain tissue and skull.

Tsao et al. 2014	n.s.	n.s.	Automated	Corticomotor tracts	Seeding randomly over the entire brain. Streamlines traversing the posterior limb of internal capsule and ended in one of the 34 cortical regions were extracted from the whole brain tractogram.
Tsao et al. 2015	n.s.	n.s.	Automated	Thalamocortical tracts	Seeding randomly over the entire brain. Streamlines traversing the thalamus and ended in one of the 34 cortical regions in each hemisphere were extracted from the whole brain tractogram.
Wang et al. 2014	0.15	60°	Manual	SCP, MCP, CST	For the SCP, ROI 1 was placed in the coronal plane passing through the tip of the central lobule of the cerebellum. ROI 2 was placed posterior to the medial longitudinal fasciculus in the axial plane. The MCP is generated from single ROIs on the coronal view. For the CST, ROI 1 was drawn in the longitudinal pontine fibers and ROI 2 in the primary motor cortex.
Weinstein et al. 2014	0.25	70°	Manual	PLIC, CC, CST	The CC was extracted using one ROI defined on a mid-sagittal FA image with further subdivision into three segments based on Witelson parcellation scheme (i.e. genu, midbody and splenium). For the CST, three ROI were drawn in the unilateral pons, posterior limb of the internal capsule and motor and premotor cortex.
Weinstein et al. 2015	0.25	70°	Manual	CC, CST	A multiple ROI approach was used to track the the CST: unilateral pons, posterior limb of the internal capsule and motor and premotor cortex.
Weinstein et al. 2018	0.2	70°	Manual	CC and CST	The CC was extracted using one ROI defined on a mid-sagittal FA image with further subdivision into three segments based on Witelson parcellation scheme (i.e. genu, midbody and splenium). For the CST, three ROI were drawn in the unilateral pons, posterior limb of the internal capsule and motor and premotor cortex.

ROI, region of interest; CST, corticospinal tract; ML, medial lemniscus; PLIC, posterior limb of internal capsule; ACC, anterior cingulate cortex; SCP, superior cerebellar peduncle; MCP, middle cerebellar peduncle; CC, corpus callosum; VBA, voxel-based analysis; WM; white matter; n.s., not specified.