Received: 14 April 2022 | Accepted: 13 December 2022

DOI: 10.1111/dmcn.15516

SCOPING REVIEW

Brain structural and functional connectivity and network organization in cerebral palsy: A scoping review

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Funding information
European Commission (Horizon 2020) - Marie Skłodowska-Curie fellow, Grant/Award Number: 660458; Gerrit Jan van Ingen Schenau Promising Young Scientist Award, Grant/Award Number: NA; Phelps Foundation for Spasticity, Grant/Award Number: 2016025; Research Foundation Flanders, Grant/Award Number: 1503915N

Abstract

Aim: To explore altered structural and functional connectivity and network organization in cerebral palsy (CP), by clinical CP subtype (unilateral spastic, bilateral spastic, dyskinetic, and ataxic CP).

Method: PubMed and Embase databases were systematically searched. Extracted data included clinical characteristics, analyses, outcome measures, and results.

Results: Sixty-five studies were included, of which 50 investigated structural connectivity, and 20 investigated functional connectivity using functional magnetic resonance imaging (14 studies) or electroencephalography (six studies). Five of the 50 studies of structural connectivity and one of 14 of functional connectivity investigated whole-brain network organization. Most studies included patients with unilateral spastic CP; none included ataxic CP.

Interpretation: Differences in structural and functional connectivity were observed between investigated clinical CP subtypes and typically developing individuals on a wide variety of measures, including efferent, afferent, interhemispheric, and intrahemispheric connections. Directions for future research include extending knowledge in underrepresented CP subtypes and methodologies, evaluating the prognostic potential of specific connectivity and network measures in neonates, and understanding therapeutic effects on brain connectivity.

Abbreviations: DTI, diffusion tensor imaging; DWI, diffusion-weighted magnetic resonance imaging.

Cerebral palsy (CP) is an umbrella term encompassing impairment in movement, posture, or muscle tone, caused by a heterogeneous group of underlying brain disorders occurring in early development.[1] With a prevalence of about 1 to 2.5 per 1000 live births, CP is the most frequent motor disorder in children in the Western world.[1] Depending on the localization of the brain abnormalities, three clinical subtypes of CP can be distinguished, of which spastic CP is the most common subtype (about 84%), followed by dyskinetic CP (about 13%) and ataxic (about 3%) CP.[2] Within these groups, individual impairments are very diverse, for example with respect to type and severity of functional disabilities.

Diagnosing an individual with CP requires a multidisciplinary approach, including clinical observation, and usually radiological assessment of conventional structural brain magnetic resonance imaging (MRI), such as T1- and T2-weighted images. These images are helpful in revealing the underlying cause of CP in the individual, such as periventricular leukomalacia, damage to deep grey matter, or cortical malformation,[3,4] and may have implications for further diagnostic examinations, such as genetic testing. Early conventional MRI is also used to aid in prognostication. Accurate prognostication in neonates or young children is critical, not only to adequately inform parents at an early stage but also to facilitate early treatment interventions to enhance the functioning of patients. However, predictive use of conventional MRI has its limitations, mostly due to the widespread range in brain abnormalities and possible outcomes, which do not always correspond with each other.[5–7] For instance, children with periventricular leukomalacia on conventional MRI do not necessarily develop motor problems, and thus will not all develop CP.[8]

Advanced neuroimaging modalities have the potential to improve our understanding of the relationship between brain (dys)function and clinical manifestations. Diffusion-weighted MRI (DWI), functional MRI (fMRI), and electroencephalography (EEG) can be used to examine brain connectivity and network organization. The term 'connectivity' is used to describe how well specific brain regions are interconnected, and it encompasses 'structural' and 'functional' connectivity. Structural connectivity refers to regional white matter arrangement and can be investigated using DWI. To extract features from DWI, various models can be applied, of which the diffusion tensor imaging (DTI) model is the most well-known. DTI enables calculation of the diffusion tensor within every voxel, from which a variety of measures can be extracted that are usually interpreted as reflecting white matter microstructure. A common DTI-derived measure is fractional anisotropy, quantifying the directionality of diffusion. Fractional anisotropy reflects a complex relationship of both axial diffusivity, parallel to the main diffusion direction ('along the white matter tracts'), and radial diffusivity, perpendicular to the main diffusion direction. When diffusion is isotropic (for instance in cerebrospinal fluid), axial diffusivity and radial diffusivity have a similar magnitude and fractional anisotropy is close to 0. In bundles with white matter tracts, radial diffusivity is lower than axial diffusivity, owing to the small spaces between axons, and fractional anisotropy approaches values of 1, indicating highly anisotropic diffusion.[9] Mean diffusivity (also called apparent diffusion coefficient, or trace) is a measure of overall diffusivity, and is a linear combination of axial diffusivity and radial diffusivity. Although all four measures can be derived from the tensor, fractional anisotropy is most often reported. During development, mean diffusivity and radial diffusivity typically decrease and fractional anisotropy increases, whereas changes in axial diffusivity are more variable.[10] Although there is no unique relationship between a single DTI measure and the underlying tissue microstructure, changes in radial diffusivity and fractional anisotropy are often interpreted in relation to myelination, while other developmental cellular changes, including axonal packing, also affect axial diffusivity and mean diffusivity.[9,10] However, although higher fractional anisotropy values are generally interpreted as an indication of better white matter microstructure, this interpretation requires caution, also due to a multitude of fibre orientations within a single imaging voxel (crossing/kissing/fanning fibres).[11] In general, DWI-derived measures (including DTI-derived measures) can be investigated using several methods, including whole brain or white matter skeleton voxel-based analyses (e.g. tract-based spatial statistics), analyses based on region of interest to investigate specific white matter regions, and diffusion tractography analyses to examine specific white matter tracts.

Functional connectivity can be estimated using various imaging modalities, including fMRI (by measuring the temporally correlated variation of the BOLD signal of anatomically separated brain regions) and EEG (by measuring temporally correlated electrical activity of brain regions). This connectivity can be investigated using model-based methods, such as seed-based analyses to investigate correlation coefficients or coherences between a-priori-defined 'seed' regions and other voxels, and data-driven methods, such as independent component analysis and data complexity analysis.[12]

The term 'brain network organization' is used to describe structural or functional brain connectivity on a large scale,

What this paper adds

- Structural and functional brain connectivity and network organization are altered in cerebral palsy (CP).
- Those alterations vary between clinical CP subtypes.
- Connectivity can be altered also in patients with CP with normal conventional magnetic resonance imaging.
- Lower fractional anisotropy in CP typically coincides with higher radial diffusivity in the corticospinal tract.

typically of the whole brain, although reconstruction of explicitly specified networks (such as a 'motor network') is also possible. Brain networks are usually reconstructed on the basis of the principles of graph theory, which implies that the connections (referred to as 'edges' in network studies) between brain regions (referred to as 'nodes') are investigated in a pairwise manner.[13–15] Exact definition of edges and nodes is critical for brain network analysis. Nodes are typically defined as a specific group of neurons or regions of interest of the brain that can be adequately localized. Edges represent connectivity between certain nodes, and may be unweighted (i.e. either absent or present) or weighted, taking into account the value (strength) of the connection, such as fractional anisotropy or streamline density in structural analyses, or BOLD correlation coefficients in functional analyses.[16,17] Common metrics derived from graph theory to describe brain networks include efficiency, clustering coefficient, and small-worldness (see, for example, van Straaten and Stam[17]).

In recent years, there has been increased awareness that brain connectivity and network organization are important for brain functioning, both in healthy and diseased brains.[18–20] Multiple studies have investigated structural and functional brain connectivity and network organization in CP. Assuming that brain connectivity and network organization may be disrupted in CP, this information would improve our understanding of CP-related brain alterations, beyond what is known from conventional MRI studies. Eventually, this knowledge could be used towards unravelling the relationship between altered brain connectivity, network organization, and functional outcomes in CP. This could ultimately be used to improve prognostication or as a marker to investigate therapeutic effects. Structural connectivity in CP has been reviewed previously by Scheck et al.,[21] but many studies have investigated structural connectivity in CP since 2012. To the best of our knowledge, functional connectivity and network organization in CP have not been reviewed previously, indicating that the landscape of studies in this domain in CP is relatively unexplored. Therefore, the aim of this scoping review was to provide an overview of studies in this domain, and summarize and discuss what is known about structural and functional brain connectivity and network organization in CP. Subsequently, results of this review can be used as a handle for future (systematic) reviews and clinical trials.

METHOD

The methodology of the JBI handbook for scoping reviews was used as guidance for this review.[22] Reporting was done in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines.[23] A protocol of this review was previously registered at PROSPERO (registration number CRD42020124696), as a systematic review and later adjusted to meet the requirements of a scoping review.

Search methods

A comprehensive search was performed in the bibliographic databases PubMed and Embase from inception to 20th September 2021, in collaboration with a medical librarian (LJS). Search terms included controlled terms (MeSH in PubMed, Emtree in Embase) as well as free-text terms. The following inclusion terms were used (including synonyms and closely related words) as index terms or free-text words: 'cerebral palsy' AND ('diffusion magnetic resonance imaging' OR 'functional near infrared imaging' OR ['brain connectivity' AND 'magnetic resonance imaging'/electroencephalography/magnetoencephalography]). The search was performed without date or language restrictions. Duplicate articles were excluded. Full search strategies for both databases can be found in Appendix S1.

Study inclusion

All titles and abstracts were carefully read by two independent researchers. The following inclusion criteria were applied: (1) a comparison was performed between individuals with CP and typically developing individuals or between both hemispheres in individuals with unilateral CP; (2) the analysis performed was a structural or resting-state functional brain connectivity (or brain network) analysis, using one of the techniques of DWI, fMRI, EEG, magnetoencephalography, or functional near-infrared spectroscopy; (3) corresponding outcome parameters were quantitative and statistically analysed; (4) written in English. The following exclusion criteria were applied: (1) unavailability of full text; (2) case studies, defined as three or fewer individuals with CP; (3) conference abstracts, reviews, commentaries, dissertations, or study protocols; (4) animal studies; (5) absence of a diagnosis of CP for one or more patients at the moment the data were collected. To include or exclude abstracts, the researchers made use of 'Covidence', an online systematic review platform (https://www.covidence.org). After abstract selection, the full texts of all included studies were read by two independent researchers (NPTJ and LAvdP) to ensure correct eligibility for inclusion in the review. In the case of disagreement between researchers, both re-read the corresponding abstract or full text and, after discussion, reached consensus. Reference lists of all included articles were systematically assessed for relevant articles that were not included through the search on PubMed and Embase.

Data extraction and analysis

Data were extracted using a standardized form specifically developed for this review. Data extraction included the following headings: design, participants, measurement protocol, brain connectivity or network analysis, regions of interest, outcome measure(s), results, discussion, and other comments. Patients with CP were classified into one of five

subtypes: unilateral spastic CP, bilateral spastic CP, dyskinetic CP, ataxic CP, and patients clinically diagnosed with CP but without abnormalities on conventional MRI. When a study investigated two CP groups within one study, both groups are described separately. When one CP group comprised multiple CP subtypes, results of that CP group were outlined towards the CP subtype that most of the patients belonged to. Type of CP was not always fully reported. In cases when only 'hemiplegia', 'unilateral', or 'diplegia' was reported, it was assumed that the spastic type was implicated. For DWI studies that applied the DTI model, our focus on outcome measures was on fractional anisotropy, tract volume, and symmetry. Fractional anisotropy was most often reported. To also investigate the effect of the diffusivity measures mean diffusivity, axial diffusivity, and radial diffusivity, we included these measures for the corticospinal tract as secondary analysis. Volume and symmetry were included because these measures do not reflect the diffusion tensor and might thus provide additional information. For DWI studies applying models other than DTI, and for functional connectivity and network studies, expectations about outcome measures were less clear. Therefore, these analyses were more explorative and included all available outcome measures.

RESULTS

The literature search identified 946 abstracts from the PubMed and 1035 abstracts from Embase. Three studies were identified through reference screening. After removal of duplicates, a total of 1547 abstracts were included for abstract selection. On the basis of the titles and abstracts, 1233 studies were excluded. After reading the full text of 314 studies, a total of 65 met all criteria and were included. A flow chart of study selection, including reasons for exclusion after reading the full text, is given in Figure S1.

Patients' characteristics and reported data

Details of patients' characteristics and reported data, summarized by study and organized by type of analysis (structural or functional connectivity or network study), are shown in Table S1. The number of included patients ranged from 4 to 70 patients per CP group, with a median of 15 patients. Sixty-two of 65 studies also included a typically developing comparison group. If no comparison group was included, the studies compared hemispheres within the CP group. The median reported age of the CP groups was 11 years 6 months (range 1 years 4 months–33 years 8 months), illustrating that most studies included children with CP, whereas a few studies included adolescents or adults with CP. Most studies included patients with unilateral spastic CP (considered a 'main' type in 32 studies), followed by bilateral spastic CP (24 studies), dyskinetic CP (eight studies), and patients clinically diagnosed with CP but without abnormalities on conventional MRI (four studies) (note that three studies included two main types in distinct analyses). None of the selected studies included patients with ataxic CP. Levels of Gross Motor Function Classification System (GMFCS)[24] were reported in 40 studies, and varied between GMFCS levels I and V, although the higher GMFCS levels (IV and V, indicating lower functional mobility) were slightly underrepresented (Table S1).

Forty-four studies investigated structural connectivity (not including network studies), of which 16 used deterministic tractography, 14 used probabilistic tractography, 13 used region of interest segmentation, and six used voxel-based analyses (of which five used tract-based spatial statistics). Forty studies applied the DTI model, one study also applied the NODDI model, and one study applied the q-sampling imaging model. The most common DTI-derived measure was fractional anisotropy (40 studies), followed by mean diffusivity (29 studies), radial diffusivity (17 studies), axial diffusivity (16 studies), volume of DTI-derived white matter tracts or white matter regions (10 studies) (and area, one study), and symmetry (six studies). NODDI-derived measures were isotropic volume fraction, intracellular volume fraction, and orientation dispersion index. Q-sampling imaging-derived measures included quantitative anisotropy, generalized fractional anisotropy, number of fibres, and volume (Table S1).

Nineteen studies investigated functional connectivity (not including network studies), of which 10 used fMRI seed-based analysis, four used EEG coherence analysis, two used EEG complexity analysis, two used fMRI independent component analysis, and one used fMRI voxel-mirrored homotopic connectivity analysis. Neither magnetoencephalography nor functional near-infrared spectroscopy studies met the inclusion criteria. The correlation coefficient was used as the outcome measure in all fMRI seed-based and voxel-mirrored homotopic analyses, of which one study also investigated the connectivity index. Interhemispheric coherence was used as outcome measure in all EEG coherence analyses, of which three studies also investigated intrahemispheric coherence. Fractal dimension and omega complexity were outcomes of EEG complexity analyses (Table S1).

Five studies investigated structural network organization, using measures of graph theory. Three studies used deterministic fibre tracking and two studies used probabilistic fibre tracking. Functional network organization was investigated by one study, using fMRI-derived partial correlation. Outcome measures of brain network studies included efficiency, clustering coefficient, degree, small-worldness, and characteristic path length (Table S1).

Structural connectivity

Fractional anisotropy results, organized by CP subtype, are shown in Table 1 and discussed below. Results of tract volume and symmetry can be seen in Appendix S2 and Tables S2 and S3 respectively. Results of the (secondary) analysis on

TABLE 1 Findings from fractional anisotropy, by cerebral palsy subtype

		Unilateral spastic CP		Bilateral spastic CP	Dyskinetic CP
Fibre type	**Tract/region**	**Ipsilesional vs contralesional hemisphere[a]**	**CP vs TDI[b]**	**CP vs TDI[c]**	**CP vs TDI[c]**
Projection fibres: efferent	Corticospinal tract	↓ (Glenn et al.[74]; Hodge et al.[76]; Kuczynski et al.[81]; Kuo et al.[82]; Papadelis et al.[87]; Scheck et al.[91]; Tsao et al.[95]) = (Nemanich et al.[25]; Thomas et al.[93])	↓↓ (Azizi et al.[68,s]; Kuczynski et al.[81,d]; Papadelis et al.[88]) ↓ = (Carlson et al.[32]; Glenn et al.[74,o]; Galli et al.[73,f]; Holmström et al.[77]; Kuczynski et al.[81,d]; Lennartsson et al.[84]; Pannek et al.[26,u]; Papadelis et al.[87]; Scheck et al.[91]; Scheck et al.[92,p]; Thomas et al.[93]; Tsao et al.[95]) == (Glenn et al.[74,o]; Weinstein et al.[99])	↓↓ (Arrigoni et al.[67]; Azizi et al.[68,s]; Chang et al.[70]; Mahanna et al.[85,t]; Trivedi et al.[27,e]; Wang et al.[97]; Wang et al.[98]) ↓ = (Trivedi et al.[27,e]) == (Fan et al.[71]; Koerte et al.[79]; Trivedi et al.[27,e]; Yoshida et al.[100]; Yoshida et al.[101]) ↓ (Condliffe et al.[28,m])	↓↓ (Laporta-Hoyos et al.[83]; Yoshida et al.[101]) == (Harlaar et al.[75]; Park et al.[89])
	Corticobulbar tract	↓ (Thomas et al.[93])	↓ = (Thomas et al.[93])	== (Wang et al.[97])	
Projection fibres: afferent	Sensory tract/dorsal column: medial lemniscus tract/ spinothalamic fibres	↓ (Tsao et al.[95]) = (Kuczynski et al.[80]; Papadelis et al.[86]; Papadelis et al.[87])	↓ = (Tsao et al.[95]) == (Kuczynski et al.[80]; Papadelis et al.[86]; Papadelis et al.[87])	== (Wang et al.[97])	
	Thalamic radiation: anterior	= (Thomas et al.[93]; Tsao et al.[96])	== (Thomas et al.[93]; Tsao et al.[96])	=↓ (Arrigoni et al.[67])	
	Thalamic radiation: superior	↓ (Tsao et al.[96]) = (Papadelis et al.[87]; Thomas et al.[93])	↓ = (Tsao et al.[96]) == (Lennartsson et al.[84]; Papadelis et al.[87]; Thomas et al.[93])	↓↓/↓=/== (Trivedi et al.[27,g])	
	Thalamic radiation: posterior	= (Thomas et al.[93])	↓↓ (Scheck et al.[92,p]) == (Thomas et al.[93]; Scheck et al.[92,p])	↓↓ (Arrigoni et al.[67]; Fan et al.[71];Wang et al.[97]; Yoshida et al.[101]) ↓ = (Yoshida et al.[100,l])	↓↓ (Yoshida et al.[101])
	Thalamic radiations: anterior, superior, and posterior			↓↓ (Mahanna et al.[85,t])	
Commissural fibres	Corpus callosum: genu	—	↓ (Scheck et al.[92,p]) = (Papadelis et al.[87]; Scheck et al.[92,p]; Thomas et al.[93]; Weinstein et al.[99])	↓ (Fan et al.[71]; Rai et al.[90]; Trivedi et al.[94]) = (Arrigoni et al.[67]; Wang et al.[97]; Yoshida et al.[101])	↓ (Laporta-Hoyos et al.[83]; Yoshida et al.[101])
	Corpus callosum: body	—	↓ (Park et al.[34]; Scheck et al.[92,p]; Thomas et al.[93]; Weinstein et al.[99]) = (Scheck et al.[92,p])	↓ (Arrigoni et al.[67])	
	Corpus callosum: splenium	—	↓ (Scheck et al.[92,p]) = (Scheck et al.[92,p]; Thomas et al.[93]; Weinstein et al.[99])	↓ (Arrigoni et al.[67]; Fan et al.[71]; Rai et al.[90];Trivedi et al.[94]; Wang et al.[97]; Yoshida et al.[101])	↓ (Yoshida et al.[101])
	Forceps minor	—	= (Kuczynski et al.[80])	= (Arrigoni et al.[67])	
	Forceps major	—		= (Arrigoni et al.[67])	
	Trans-callosal motor fibres	—		↓ (Koerte et al.[79])	
	Fornix	—		= (Arrigoni et al.[67])	
	Anterior commissure			= (Wang et al.[97])	

(Continues)

TABLE 1 (Continued)

Fibre type	Tract/region	Unilateral spastic CP		Bilateral spastic CP	Dyskinetic CP
		Ipsilesional vs contralesional hemisphere[a]	CP vs TDI[b]	CP vs TDI[c]	CP vs TDI[c]
Association fibres	Inferior longitudinal fasciculus		↓↓/== (Scheck et al.[92,p])	== (Arrigoni et al.[67]; Yoshida et al.[101])	=↓ (Yoshida et al.[101])
	Superior longitudinal fasciculus	= (Thomas et al.[93])	↓↓ (Scheck et al.[92,p]) ↓ =(Galli et al.[73,f]; Scheck et al.[92,p]) == (Scheck et al.[92,p]; Thomas et al.[93])	↓↓ (Arrigoni et al.[67]; Fan et al.[71]; Wang et al.[97]; Yoshida et al.[101]) ↑ =(Bauer and Papadelis[29,r])	↓↓ (Laporta-Hoyos et al.[83]; Park et al.[89]; Yoshida et al.[101])
	Frontal aslant tract			↑ = (Bauer and Papadelis[29,r])	
	Unicate fasciculus			↓↓ (Arrigoni et al.[67])	
	Inferior fronto-occipital fasciculus			== (Arrigoni et al.[67]; Bauer and Papadelis[29,r])	
	Cingulum	= (Scheck et al.[91]; Thomas et al.[93])	↓↓ (Scheck et al.[91,j]; Scheck et al.[92,p]) == (Scheck et al.[91,j]; Scheck et al.[92,p]; Thomas et al.[93])	↓↓ (Arrigoni et al.[67]; Fan et al.[71]) == (Wang et al.[97]; Yoshida et al.[101])	↓↓ (Yoshida et al.[101])
	Arcuate fasciculus			↓↓ (Fan et al.[71]; Wang et al.[97])	== (Harlaar et al.[75,k])
	Anterior cingulate cortex projections	↓/= (Scheck et al.[91,n])	== (Scheck et al.[91])		
	Sensorimotor U-fibres	↓ (Papadelis et al.[87])	↓ =(Papadelis et al.[87])		
Regional white matter	Corona radiata	↓ (Park et al.[34])	↓↓/↓=/== (Scheck et al.[92,p])	↓↓ (Arrigoni et al.[67,h]; Chang et al.[70]; Fan et al.[71]; Rai et al.[90];Wang et al.[97]; Trivedi et al.[94])	↓↓ (Laporta-Hoyos et al.[83,q])
	Internal capsule: anterior limb		↓↓ (Scheck et al.[92,p]) ↓ =(Holmström et al.[77]; Scheck et al.[92,p]; Weinstein et al.[99]) == (Scheck et al.[92,p])	↓↓ (Rai et al.[90]) == (Arrigoni et al.[67]; Fan et al.[71]; Wang et al.[97]; Yoshida et al.[101])	↓↓ (Yoshida et al.[101])
	Internal capsule: posterior limb		↓↓/↓ =(Scheck et al.[92,p])	↓↓ (Chang et al.[70,i]; Fan et al.[71]; Rai et al.[90];Trivedi et al.[94];Wang et al.[97]; Yoshida et al.[100]; Yoshida et al.[101]) == (Arrigoni et al.[67], Chang et al.[70,i])	↓↓ (Yoshida et al.[101])
	Internal capsule: retrolenticular part		↓↓/== (Scheck et al.[92,p])		
	External capsule		↓↓/↓ =(Scheck et al.[92,p])	↓↓ (Arrigoni et al.[67]) == (Wang et al.[97])	
	Cerebral peduncle		↓↓ (Scheck et al.[92,p]) ↓ =(Holmström et al.[77]; Scheck et al.92[,p])		
	Cerebellar peduncle: inferior			↓ =(Arrigoni et al.[67])	↓↓ (Laporta-Hoyos et al.[83])

TABLE 1 (Continued)

Fibre type	Tract/region	Unilateral spastic CP		Bilateral spastic CP	Dyskinetic CP
		Ipsilesional vs contralesional hemisphere[a]	CP vs TDI[b]	CP vs TDI[c]	CP vs TDI[c]
	Cerebellar peduncle: middle		== (Thomas et al.[93])	↓↓ (Wang et al.[98]) == (Arrigoni et al.[67]; Fan et al.[71]; Wang et al.[97])	
	Cerebellar peduncle: superior			↓↓ (Arrigoni et al.[67]; Wang et al.[98]) == (Wang et al.[97])	↓↓ (Laporta-Hoyos et al.[83])
	Cerebellum		↓↓/↓=/== (Scheck et al.[92,p])		
	Medial lemniscus			== (Fan et al.[71])	↓↓ (Laporta-Hoyos et al.[83])

Abbreviations: CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; TDI, typically developing individuals.

[a]The symbol indicates whether fractional anisotropy of the ipsilesional hemisphere is reduced (↓), unaltered (=), or increased (↑) compared with the contralesional hemisphere.

[b]The first symbol indicates whether fractional anisotropy in the ipsilesional hemisphere is altered compared with TDI; the second symbol indicates whether fractional anisotropy in the contralesional hemisphere is altered compared with TDI.

[c]The first symbol indicates whether fractional anisotropy in the left hemisphere is altered compared with TDI; the second symbol indicates whether fractional anisotropy in the right hemisphere is altered compared with TDI.

[d]Lower in both hemispheres for children with CP with arterial ischemic stroke but not for children with CP with periventricular venous infarction.

[e]Lower fractional anisotropy in bilateral corticospinal tract for GMFCS level V, no differences in fractional anisotropy for bilateral corticospinal tract in GMFCS level IV, unilaterally lower fractional anisotropy (left) in corticospinal tract for GMFCS level II.

[f]Instead of a comparison between affected and unaffected, a comparison between left and right was made.

[g]Lower fractional anisotropy in bilateral thalamic radiation superior for GMFCS level V, unilaterally lower fractional anisotropy in thalamic radiation superior for GMFCS level IV, no differences in fractional anisotropy in thalamic radiation superior for GMFCS level II.

[h]Lower fractional anisotropy in corona radiata superior and posterior parts, but not in anterior part.

[i]Lower fractional anisotropy for quadriplegic CP, but not for diplegic CP.

[j]Fractional anisotropy of cingulum was lower for left-sided unilateral CP but not for right-sided unilateral CP.

[k]Arcuate fasciculus tract could not be visualized in all patients with CP.

[l]Results are shown for tractography analysis, lower fractional anisotropy was observed for both sides when using region of interest segmentation analysis.

[m]Only the corticospinal tract corresponding to the leg that interfered most with function was investigated.

[n]Lower fractional anisotropy for projections to superior frontal gyrus, but not medial orbitofrontal gyrus, precuneus, or rostral middle frontal gyrus.

[o]Lower fractional anisotropy in lesioned hemisphere in moderate and severe hemiparesis, but not in mild hemiparesis.

[p]Various results; for results by type of CP see Scheck et al.[92]

[q]Anterior part of corona radiata.

[r]Generalized fractional anisotropy, derived from q-sampling imaging.

[s]It is not mentioned how many children belonged to the bilateral vs unilateral group, so comparisons with TDI included in both columns. Results of ipsilesional vs contralesional hemisphere are therefore not included in this table.

[t]Given that most participants were classified in GMFCS levels IV or V, it is assumed that the bilateral group was implicated.

[u]Tracts were investigated using a connectome approach. To minimize bias in explicitness of tracts that are not significantly different, only results for the corticospinal tract are indicated in this table; other results are described in the Results section.

mean diffusivity, axial diffusivity, and radial diffusivity, in relation to observations for fractional anisotropy within the corticospinal tract, are shown in Table S4.

In unilateral spastic CP, 22 studies investigated fractional anisotropy (Table 1), seven investigated volume (Table S2), and five investigated symmetry (Table S3). For unilateral spastic CP, the term 'ipsilesional' is used to refer to the hemisphere where the lesion occurred, so contralateral to the participant's affected body side. The term 'contralesional' is used to refer to the hemisphere ipsilateral to the participant's affected body side. Fractional anisotropy of efferent projection fibres (corticospinal tract and corticobulbar tract) of the ipsilesional hemisphere of individuals with unilateral spastic CP was usually lower than both the contralesional hemisphere (8 out of 10 evaluations) and typically developing individuals (16 out of 18 evaluations). Volume of the corticospinal tract of the ipsilesional hemisphere of individuals with CP was also reduced, compared with both the contralesional hemisphere (four out of four studies) and typically developing individuals (three out of three studies). Fractional anisotropy and volume of the corticospinal tract of the contralesional hemisphere were usually unaltered compared with typically developing individuals (14 out of 17 and three out of three evaluations respectively). Three studies reported increased asymmetry in fractional anisotropy or volume of the corticospinal tract between hemispheres in CP compared with typically developing individuals. For the afferent projection fibres, fractional anisotropy of the ipsilesional hemisphere of the CP group was mostly unaltered, compared with both the contralesional hemisphere (8 out of 10 evaluations) and typically developing individuals (10 out of 13 evaluations). Results of volume of the afferent projection fibres of the ipsilesional hemisphere were more variable, as reduced volume was observed in three out of six evaluations compared with both the contralesional hemisphere and typically developing individuals. For commissural fibres, fractional anisotropy of the body of the corpus callosum was typically reduced in CP compared with typically developing individuals (four out of five evaluations), whereas fractional anisotropy of the genu and the splenium of the corpus callosum were mostly unaltered (four out of five and three out of four evaluations respectively). Volume of the body of corpus callosum was reduced in CP in one out of two studies. For the association fibres, we observed no reduction in fractional anisotropy of the cingulum of the ipsilesional hemisphere compared with the contralesional hemisphere of the CP group (two out of two studies), but results were inconsistent compared with typically developing individuals (Table 1). Results of fractional anisotropy of the superior longitudinal fasciculus of the ipsilesional hemisphere compared with typically developing individuals were inconsistent as well (Table 1). Volumes of the superior longitudinal fasciculus and the cingulum of the ipsilesional hemisphere of the CP group were unaltered compared with the contralesional hemisphere (three out of three evaluations) and typically developing individuals (three out of three evaluations). Few studies investigated fractional anisotropy of specific white matter regions, with inconsistent results (Table 1). Finally, Nemanich et al.[25] applied the NODDI model beside the DTI model, and found lower intracellular volume fraction and orientation dispersion index in the ipsilesional corticospinal tract compared with the contralesional corticospinal tract, while no differences were observed for isotropic volume fraction. Using the connectome approach, Pannek et al.[26] investigated fractional anisotropy of tracts in unilateral CP compared with typically developing individuals, and found various differences, including lower fractional anisotropy in ipsilesional corticospinal connections, motor thalamocortical connections, and association connections, compared with typically developing individuals.

In bilateral spastic CP, 15 studies investigated fractional anisotropy (Table 1), of which three also investigated volume (Table S2). No studies investigated symmetry. Results of fractional anisotropy in the corticospinal tract of individuals with bilateral spastic CP were inconsistent: seven studies indicated reduced fractional anisotropy compared with typically developing individuals in both hemispheres, and five found no differences between those with CP and typically developing individuals in both hemispheres. One study, assessing both hemispheres in bilateral spastic CP, found reduced fractional anisotropy only in the left hemisphere.[27] Another study studied only one hemisphere, corresponding to the side of the leg that interfered most with function and found reduced fractional anisotropy in the contralateral hemisphere[28] (Table 1). The volume of the corticospinal tract was reduced in both hemispheres compared with typically developing individuals (two out of two studies). Fractional anisotropy of posterior thalamic radiation was typically reduced compared with typically developing individuals, at least in one hemisphere (five out of five evaluations). For the commissural fibres, a reduction in fractional anisotropy of genu, body, and splenium of the corpus callosum in the CP group was reported in three out of six, one out of one, and six out of six studies respectively. For the association fibres, fractional anisotropy of the superior longitudinal fasciculus was reduced (four out of four studies) and fractional anisotropy of inferior longitudinal fasciculus was unaltered (two out of two studies). Fractional anisotropy of the cingulum was reduced in two out of four studies. For white matter regions, fractional anisotropy of the corona radiata and the posterior limb of the internal capsule were usually reduced (six out of six and seven out of nine evaluations respectively). Results of fractional anisotropy in the cerebellar peduncles were ambiguous (Table 1). Lastly, Bauer and Papadelis,[29] applying the q-sampling imaging model, found increased mean generalized fractional anisotropy for the left superior longitudinal fasciculus and left frontal aslant tract, and reduced volume for the bilateral superior longitudinal fasciculus, in CP compared with typically developing individuals.

In dyskinetic CP, four studies investigated fractional anisotropy (Table 1), of which two also investigated volume (Table S2). No studies investigated symmetry in dyskinetic

CP. Compared with typically developing individuals, fractional anisotropy and volume of the corticospinal tract of individuals with dyskinetic CP was lower in two out of four studies and one out of two studies respectively. Fractional anisotropy of the genu of the corpus callosum was lower in two out of two studies. Lower fractional anisotropy of the superior longitudinal fasciculus was reported in three out of three studies. Fractional anisotropy of the arcuate fasciculus was similar between those with CP and typically developing individuals, but the volume of the arcuate fasciculus was decreased in CP (one out of one study). Furthermore, widespread lower fractional anisotropy values were reported, including posterior thalamic radiation, splenium of the corpus callosum, inferior longitudinal fasciculus, anterior and posterior limb of the internal capsule, cingulum, and cerebellar peduncles (Table 1).

In individuals with spastic bilateral CP whose conventional MRI showed no abnormalities, Mu et al.[30] found reduced fractional anisotropy compared with typically developing individuals in the prefrontal lobe, temporal lobe, internal capsule, external capsule, corpus callosum, cingulum, thalamus, brain stem, and cerebellum, making use of tract-based spatial statistics. In individuals with spastic unilateral CP whose conventional MRI showed no abnormalities, Son et al.[31] found increased asymmetry in fractional anisotropy of the corticospinal tracts above the level of the lesion of corona radiata, compared with typically developing individuals.

For all evaluations within the corticospinal tract, we analysed whether changes in fractional anisotropy were related to changes in mean diffusivity, axial diffusivity, and/or radial diffusivity (Table S4). Radial diffusivity results, reported in 21 out of 44 evaluations, were highly concordant with fractional anisotropy: 18 out of 21 evaluations were consistent, namely a lower fractional anisotropy in one or two corticospinal tract sides coincided with a higher radial diffusivity (16 evaluations) in these side(s), or the absence of any change in fractional anisotropy coincided with the absence of any change in radial diffusivity (two evaluations). Partial consistency (consistency in only one of the hemispheres) in individuals with unilateral CP was observed in two evaluations, while only one study showed no consistency (i.e. higher radial diffusivity, while no change in fractional anisotropy was detected). Mean diffusivity (or apparent diffusion coefficient, or trace) was reported in 34 out of 44 evaluations, of which 20 evaluations had a result consistent with fractional anisotropy (17 with a lower fractional anisotropy and corresponding higher mean diffusivity, and three without changes in either fractional anisotropy or mean diffusivity); nine evaluations were partly consistent, and five evaluations were inconsistent: three showing a lower fractional anisotropy, but no difference in mean diffusivity, and two showed a higher mean diffusivity, without a difference in fractional anisotropy. Axial diffusivity was reported in 19 out of 44 evaluations, and these data were more ambivalent: lower fractional anisotropy coincided with higher, lower, and absence of differences in axial diffusivity (Table S4).

Functional connectivity

Results of functional connectivity, organized by type of CP, are summarized in Table 2 (fMRI) and Table 3 (EEG).

In unilateral spastic CP, eight studies investigated functional connectivity, using fMRI (six studies) or EEG (two studies). fMRI studies indicated reduced connectivity when seeding from various brain regions, including motor, thalamic, and language-associated regions.[32–36] Increased connectivity was found in the default mode network posterior component in children with CP due to arterial ischemic stroke, but not in CP due to perinatal venous infarction, compared with typically developing children.[37] Using EEG, widespread increases and decreases in inter- and intrahemispheric connectivity were reported, in various frequency bands.[38,39]

In bilateral spastic CP, eight studies investigated functional connectivity, using fMRI (five studies) or EEG (three studies). Using fMRI, regions with both increased and reduced connectivity were reported, when seeding from motor and thalamic regions.[8] Connectivity between somatosensory parts of the parietal cortex was increased.[40] Independent component analysis indicated reduced connectivity in the cerebellum network, sensorimotor network, and left lateral fronto-parietal network in CP.[41] Also, reduced connectivity was observed in some areas between the visual network and sensorimotor and auditory regions,[42] while differences in connectivity within the visuomotor network were not significant in another study.[29] Using EEG, both increases and decreases in inter- and intrahemispheric connectivity in CP were reported.[43] EEG complexity analysis indicated reduced connectivity in multiple brain regions and frequency bands in CP.[44,45]

In dyskinetic CP, four studies investigated functional connectivity, using fMRI (three studies) or EEG (one study). Reduced interhemispheric connectivity was observed in motor, sensorimotor, and premotor-related areas, and parts of frontal and calcarine areas.[46,47] Independent component analysis of fMRI data revealed reduced connectivity in the cerebellum network, sensorimotor network, and left lateral fronto-parietal network in CP.[41]

In children with spastic bilateral CP whose conventional MRI showed no abnormalities, Mu et al.[48] used fMRI to investigate functional connectivity compared with typically developing individuals. Results indicated both regions of increased connectivity and regions of reduced connectivity when seeding from anterior central gyrus and thalamus, compared with typically developing individuals.

Network organization

In unilateral spastic CP, whole-brain structural network organization was investigated by Craig et al.[49] who studied whole-brain structural connectivity, weighted by the number of streamlines, in children with unilateral CP due to arterial ischemic stroke and periventricular venous infarction

TABLE 2 Functional connectivity derived using functional magnetic resonance imaging

Reference	CP subtype	Seed regions of interest/ investigated regions	Main findings
Carlson et al.[33]	Unilateral spastic	Bilateral inferior frontal gyrus Bilateral posterior superior temporal gyrus Bilateral frontal pole	Reduced interhemispheric connectivity between inferior frontal gyri in right hemispheric stroke, but not left hemispheric stroke, compared with TDI Reduced intrahemispheric connectivity in ipsilesional hemisphere compared with contralesional hemisphere in left hemispheric stroke, but not right hemispheric stroke
Carlson et al.[32]	Unilateral spastic	Bilateral primary motor (M1) Bilateral primary sensory (S1) Bilateral SMA Bilateral thalamus Bilateral caudate Bilateral pallidum Bilateral putamen	For cortical regions, lower functional connectivity mainly between lesioned and non-lesioned M1, S1, and SMA in CP AIS group compared with TDI and CP PVI For subcortical regions, lower functional connectivity mainly in AIS compared with TDI and CP PVI for interhemispheric connectivity, but not for intrahemispheric connectivity Lower functional connectivity between cortical and subcortical regions for lesioned putamen and M1, S1, and SMA for CP AIS compared with TDI and CP PVI Overall for CP PVI, resting-state connectivity was largely similar compared with TDI
Ilves et al.[37]	Unilateral spastic	13 independent components (probabilistic ICA-derived)	Increased connectivity in default mode network posterior component in left periventricular area in CP due to AIS, but not CP due to PVI, compared with TDI
Park et al.[34]	Unilateral spastic	Ipsilesional primary motor cortex	Reduced connectivity between specific regions of the ipsilesional paracentral gyrus, and ipsilesional cingulate motor area and supplementary motor area, bilateral thalamus, and contralesional motor areas, compared with TDI
Saunders et al.[35]	Unilateral spastic	Bilateral primary motor cortex	Reduced connectivity between primary motor cortex and contralateral supplementary motor area, both when seeding from the lesioned and non-lesioned primary motor cortex, compared with TDI
Woodward et al.[36]	Unilateral spastic	Bilateral precentral gyrus Bilateral postcentral gyrus Bilateral supplementary motor cortex Bilateral thalamus	Reduced interhemispheric connectivity between thalami, compared with TDI
Bauer and Papadelis[29]	Bilateral spastic	Bilateral primary visual (V1) Bilateral lingual gyrus (V2) Bilateral primary motor (M1) Bilateral superior parietal lobe Bilateral pars opercularis and pars triangularis of inferior frontal gyrus	No significant differences in connectivity between regions in the visuomotor network in CP compared with TDI
Burton et al.[40]	Bilateral spastic	Bilateral postcentral sulcus Bilateral postcentral gyrus Bilateral posterior postcentral gyrus Left parietal operculum Left medial postcentral gyrus Bilateral inferior intraparietal sulcus Bilateral superior intraparietal sulcus	Increased connectivity between somatosensory parts of the parietal cortex compared with TDI
Doucet et al.[42]	Bilateral spastic (most)	Left precentral cortex Left lingual gyrus Left Heschl gyrus	Reduced connectivity between the visual network and regions both within the sensorimotor and auditory networks in CP compared with TDI
Lee et al.[8]	Bilateral spastic	Bilateral motor cortex Bilateral thalamus	Increased connectivity between motor cortex and adjacent parietal area, but decreased connectivity with bilateral somatosensory cortex, paracentral lobule, pre-supplementary motor area, cingulate motor area, visual cortex, superior, and inferior parietal lobules, compared with TDI Increased connectivity between thalamus and parietal, occipital, prefrontal, and posterior cingulate, but decreased connectivity with caudate nucleus, anterior and posterior cingulate cortex, and cerebellum, compared with TDI

TABLE 2 (Continued)

Reference	CP subtype	Seed regions of interest/ investigated regions	Main findings
Qin et al.[41]	Bilateral spastic	14 independent components (ICA-derived)	Reduced connectivity within the cerebellum network, sensorimotor network, and left lateral fronto-parietal network, compared with TDI Increased and reduced connectivity in the salience network compared with TDI Four disconnections between network components, compared with TDI
Qin et al.[41]	Dyskinetic	14 independent components (ICA-derived)	Reduced connectivity within the cerebellum network, sensorimotor network, and left lateral fronto-parietal network, compared with TDI Increased and reduced connectivity in the salience network compared with TDI Six disconnections between network components, compared with TDI
Qin et al.[47]	Dyskinetic	Each pair of symmetric interhemispheric voxels	Reduced interhemispheric connectivity mainly in motor and premotor-related areas, including cerebellum, precentral, supplementary motor area, anterior cingulate, middle cingulate, and bits of frontal and calcarine areas, compared with TDI
Mu et al.[48]	Bilateral spastic, without abnormalities on conventional magnetic resonance imaging	Bilateral anterior central gyrus Bilateral thalamus	Increased connectivity between anterior central gyri and contralateral precentral gyrus, postcentral gyrus, supplementary motor area, and ipsilateral postcentral gyrus, but reduced connectivity with bilateral fusiform gyrus and lingual gyrus, compared with TDI Increased connectivity between thalami and bilateral precentral gyrus, contralateral cerebellum, and inferior temporal gyrus, but reduced connectivity with bilateral basal ganglia, cingulate, and prefrontal cortex, compared with TDI

Abbreviations: AIS, arterial ischemic stroke; CP, cerebral palsy; ICA, independent component analysis; PVI, periventricular venous infarction; SMA, supplementary motor areas; TDI, typically developing individuals.

compared with typically developing individuals. Global and local efficiency, assortativity, hierarchical coefficient of regression, and small-worldness ratio were all higher in arterial ischemic stroke and periventricular venous infarction than in typically developing individuals. Also, values in the arterial ischemic stroke group were usually higher than in the group with periventricular venous infarction.

In bilateral spastic CP, whole-brain structural and functional network organization was investigated by Lee et al.[50] who found lower global and local efficiency compared with typically developing individuals in structural networks of the whole brain (weighted by the number of streamlines), but not for the functional networks. Similar observations were done for the dorsal and ventral visual stream subnetworks, but in the motor subnetwork the functional connections were more deviant than the structural ones.

In dyskinetic CP, whole-brain structural network organization was investigated by Ballester-Plané et al.[51] who concluded a globally reduced number of streamlines in CP, widespread throughout the brain, and most prominently in temporal and occipital lobes. Reductions of fractional anisotropy were more restricted to bilateral precentral, postcentral, superior parietal, and middle temporal cortices; right paracentral cortex, posterior cingulate, and superior temporal cortex; and left hippocampus, while prefrontal regions were relatively preserved.

Duan et al.[52] investigated whole-brain structural network organization in individuals with spastic bilateral CP without abnormalities on conventional MRI. The authors found that global efficiency was decreased and normalized characteristic path length was increased, which was interpreted as decreased efficiency of information transfer compared with typically developing individuals. Zhang et al.[53] also investigated structural network organization in individuals diagnosed with bilateral spastic CP without abnormalities on conventional MRI, and found multiple changes in whole-brain network measures, including a lower nodal clustering coefficient and higher nodal path lengths in various brain regions. Overall, the results were interpreted by the authors as indicating a more inefficient information exchange than in typically developing individuals.

DISCUSSION

This scoping review summarizes studies investigating differences in structural and functional connectivity and network organization in CP compared with typically developing individuals, or between hemispheres in the case of unilateral CP. Most studies focused on structural connectivity, followed by functional connectivity and network organization. Between studies, large variation in patients' characteristics

TABLE 3 Functional connectivity derived using electroencephalography

Reference	CP subtype	Number of scalp electrodes	Frequency bands	Resting state	Regions of interest	Main findings
Kulak and Sobaniec[38]	Unilateral spastic	14	Delta, theta, alpha, beta 1, beta 2	Lying, eyes closed	Whole brain	Reduced ICoh in several derivations in the alpha, delta, beta 1, and beta 2 bands for right-sided unilateral CP, reduced ICoh in the alpha, theta, delta, beta 1, and beta 2 bands for left-sided unilateral CP Increased ICoh in several derivations in the theta, delta, beta 1, and beta 2 bands for right-sided unilateral CP, increased ICoh in the beta 1 band for left-sided unilateral CP Widespread increases and reductions in HCoh were reported for both right- and left-sided unilateral CP, in various derivations and frequency bands, compared with TDI
Kułak et al.[39]	Unilateral spastic	14	Delta, theta, alpha, beta 1, beta 2	Lying, eyes closed	Whole brain	Reduced ICoh in alpha, theta, delta, beta 1, and beta 2 bands, and increased ICoh in theta, delta, beta 1, and beta 2 bands, compared with TDI Widespread increases and reductions in HCoh were reported in various derivations and frequency bands, compared with TDI
Gao et al.[44]	Bilateral spastic	20	Delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma 1, gamma 2	Sitting, eyes closed	Whole brain, anterior region, posterior region	Increased global omega complexity in alpha 2 band, compared with TDI Increased regional omega complexity in delta, theta, and alpha 1 bands, compared with TDI
Koeda and Takeshita[43]	Bilateral spastic	12	Delta, theta, alpha, beta	Lying, eyes closed	Whole brain	Reduced ICoh in occipital regions (alpha band), and increased ICoh in frontal regions (theta band), compared with TDI Increased HCoh in delta, theta, and beta bands, in several derivations, compared with TDI
Sajedi et al.[45]	Bilateral spastic	19	1–30 Hz	Sitting, eyes closed	Anterior region, central region, posterior region	Increased fractal dimension in anterior region, compared with TDI
Kukke et al.[46]	Dyskinetic	19	Delta, theta, alpha, beta	Sitting, eyes open, fixating on cursor in centre of screen	Sensorimotor cortices (C3–C4)	Reduced ICoh between sensorimotor cortices in alpha, beta, delta, and theta bands, compared with TDI

Abbreviations: CP, cerebral palsy; HCoh, intrahemispheric coherence; ICoh, interhemispheric coherence; TDI, typically developing individuals.

and methodology was observed. With regard to patients' characteristics, differences were observed between CP subtypes (unilateral or bilateral spastic CP, dyskinetic CP), severity of CP (GMFCS level), and underlying aetiologies (e.g. periventricular leukomalacia, arterial ischemic stroke, or damage to deep grey matter), reflecting that CP is an umbrella term comprising a diverse population. With regard to methodology, substantial variability was observed in choice of brain imaging modalities, type of analyses, investigated regions of interest, and outcome measures. Still, widespread alterations in connectivity and network organization were described in CP.

The results of our scoping review are in line with most of the findings of the earlier systematic review by Scheck et al.[21] for children with spastic CP. Scheck et al.[21] previously stated the involvement of the descending corticospinal tract in CP, in their review addressing structural connectivity in CP, as assessed by DTI. In addition, they mentioned a probable role for the ascending sensorimotor tracts in CP as well, although these tracts were studied in a more limited number of studies. Results of the current review are also in line with the typical occurrence of lower fractional anisotropy (and smaller volume and higher asymmetry indices) of the corticospinal tract (including posterior limb of internal capsule and/or corona radiata) in spastic CP, indicating that the architecture of the corticospinal tract is typically altered in these individuals. In addition, the secondary analysis showed that lower fractional anisotropy in the corticospinal tract almost exclusively coincided with a finding of increased radial diffusivity and mean diffusivity, while changes in axial diffusivity were ambivalent. Furthermore, the earlier hypothesis of lower fractional anisotropy in afferent projection fibres is also confirmed by the current review, suggesting that the microstructure of these fibres can be altered in spastic CP, possibly relating to deficits in sensory organization that are common in these patients (see, for example, Lagunju et al.;[54] Nashner et al.;[55] Pavão and Rocha;[56] Sanger and Kukke[57]). For example, Hoon Jr et al.[58] found that the amount of injury to the posterior thalamic radiation was related to lower touch threshold and diminished proprioception in individuals with CP. Interestingly, we observed that the lower fractional anisotropy of afferent projection fibres may be more pronounced in bilateral spastic CP than in unilateral spastic CP (Table 1). Sensory deficits may be clearer in individuals with bilateral CP compared with unilateral CP because of differences in underlying pathology, although differences in severity of CP between included groups could also play a role. Finally, according to Scheck et al.,[21] the role of commissural and association fibres in the pathogenesis of CP still remains to be elucidated. On the basis of the common occurrence of lower fractional anisotropy in commissural fibres in the current review, it is likely that the architecture of these fibres is altered in spastic CP, for example in the body of the corpus callosum (especially in unilateral spastic CP) and the splenium of the corpus callosum (especially in bilateral spastic CP), suggesting alterations in interhemispheric communication. Interestingly, in bilateral spastic CP, lower fractional anisotropy was observed in all five studies investigating posterior thalamic radiation and in all six studies investigating splenium of the corpus callosum, compared with one in three evaluations and one in four evaluations respectively in unilateral spastic CP. These white matter tracts connect occipital brain regions with ipsilateral thalamus (posterior thalamic radiation) and contralateral occipital brain regions (the splenium of the corpus callosum). Altered microstructure of these fibres might therefore be associated with cerebral visual impairment, which is common in bilateral spastic CP.[59]

Differences in spastic CP compared with typically developing individuals were also observed for functional connectivity and network analyses. Regions with altered functional connectivity include those associated with motor control, sensory integration, and interhemispheric communication, in line with the results of the structural connectivity studies described above. The observation that alterations in white matter structure may result in functional disturbances as well is interesting as it may indicate that even focal lesions, which are common in unilateral spastic CP, could affect whole-brain functioning. Still, it remains to be investigated whether the observed alterations in functional connectivity and network organization reflect a compensatory mechanism, or whether early brain damage does actually result in such widespread alterations in functional connectivity and network organization, especially because not only decreases but also increases in functional connectivity were observed in CP compared with typically developing individuals.

Dyskinetic CP is much less prevalent than spastic CP, and has been investigated in connectivity and network studies less often. Three recent studies were identified that have investigated structural connectivity in dyskinetic CP since the review by Scheck et al.[21] In dyskinetic CP, choreoathetosis and/or dystonia are the key symptoms. Damage to the basal ganglia and/or thalamus is a typical pattern on conventional MRI, and can be limited to these structures.[60] Still, the lesion extent in these structures does not always explain the severity of choreoathetosis and/or dystonia in dyskinetic CP,[61] suggesting that other pathways or structures may be involved as well. Interestingly, three out of three studies found lower fractional anisotropy in the superior longitudinal fasciculus, indicating that this tract, probably involved in auditory processing, speech, and/or language,[62,63] is affected in dyskinetic CP. Involvement of this tract might be related to problems with speech, which are very common especially in the dyskinetic CP subtype.[64] Evidence of involvement of the corticospinal tract, as assessed by DTI, is conflicting, possibly reflecting the heterogeneity of patients with dyskinetic CP in conventional MRI results. In a part of the patients, the motor cortex is involved in the initial hypoxic–ischemic damage, in addition to involvement of the basal ganglia and/or thalamus. Furthermore, some of these patients may clinically have a more mixed type of CP with a pyramidal syndrome in addition to choreoathetosis and/or dystonia.[65] Differences between those with CP and typically developing individuals may occur in other brain regions as

well. For example, Ballester-Plané et al.[51] specifically mentioned altered structural connectivity of the hippocampus in dyskinetic CP. Hippocampal damage can typically be observed on conventional MRI when basal ganglia and thalamus lesions are severe.[60] Ballester-Plané et al.,[51] however, did not describe hippocampal lesions in the conventional MRI results. This is interesting as it indicates that connectivity of the hippocampus may be reduced in dyskinetic CP, even when hippocampal damage could not be readily observed on conventional MRI. Finally, various regions of altered functional connectivity were observed in dyskinetic CP (Tables 2 and 3), including reduced interhemispheric connectivity by fMRI and EEG.[46,47]

At least 19 studies included individuals with normal conventional MRI results. In about 14% of the individuals clinically diagnosed with CP, no abnormalities on conventional MRI were found.[4] Interestingly, in the five studies in which, specifically, individuals diagnosed with CP without abnormalities on conventional MRI were compared with typically developing individuals, differences in structural and functional connectivity and network organization were observed.[30,31,48,52,53] However, in these individuals it often remains questionable whether the cause of the motor disorder is indeed CP, defined as a non-progressive disturbance that occurred in the developing brain, or rather another underlying (yet unidentified) metabolic or genetic disorder.[66] Inclusion of these children, probably reflecting a group with heterogeneous underlying pathology, in neuroimaging studies investigating CP may therefore introduce bias. No study was found in which connectivity or network organization of patients with a diagnosis of CP without abnormalities on structural MRI was compared with patients with MRI-confirmed CP.

This review identified gaps in current knowledge, translating to recommendations for future research in this domain. First, structural connectivity was investigated far more often than functional connectivity. To unravel functional connectivity and network organization in CP, it is important that these are addressed in the future. Furthermore, no studies included participants with ataxic CP, and only a limited number of studies included participants with dyskinetic CP. For future research it is important to include all clinical types of CP to represent the full spectrum of CP. Also, detailed reporting of clinical characteristics to facilitate interpretation and generalization of the results is crucial in a heterogenous condition such as CP. Therefore, the clinical subtype, severity (GMFCS levels), and conventional MRI results should be reported in every study addressing connectivity in CP.

For future studies, we suggest being careful with including individuals with (apparently) normal conventional MRI results in brain imaging studies addressing CP, as this could be a potential source of bias. It would, however, be of interest to focus future research on comparing connectivity or network organization of patients without abnormalities on conventional MRI with MRI-confirmed CP, to gain knowledge about the differences between these populations. From a clinical perspective, interesting future directions of research also include the prognostic potential of connectivity and network measures in neonates, and the effects of therapies on connectivity and network organization. Studies including long-term clinical follow-up, and well-designed pre–post studies with relevant outcome measures, will be needed to achieve these goals. To compare studies, and to make data-pooling possible, it would be helpful to harmonize outcome measures.

A limitation of this review is the summarization of fractional anisotropy, volume, and symmetry data in a qualitative way. Because of the high number of included DTI studies and concomitant substantial variability in analysis methods, we considered it was not sensible to combine outcome measures in a more quantitative way. Also, we did not include diffusivity measures such as mean diffusivity, axial diffusivity, and radial diffusivity for all tracts, owing to the large number of studies and our aim of writing a readable overview. Still, the demonstration of these diffusivities for the studies describing the corticospinal tract convincingly showed the relationship between fractional anisotropy on the one hand and mean diffusivity and radial diffusivity on the other. Finally, in this review we used the statistical significance values that were applied in the individual studies. Hence, some of the differences between studies, in combination with differences in statistical power because of differences in group size, may have been a result of the use of stricter or less strict significance requirements.

In conclusion, this review provides an overview of studies investigating differences in structural and functional connectivity and network organization between individuals with CP and typically developing individuals. Also, it provides insights into the involvement of specific brain regions, tracts, and networks in the different CP subtypes. These results can be used as a handle for future research. Eventually, interesting applications would include evaluating the prognostic potential of specific brain connectivity and network measures, and monitoring therapeutic effects on connectivity and network organization.

FUNDING INFORMATION

The Research Foundation Flanders (FWO) under grant 1503915N and the Phelps Foundation for Spasticity under grant 2016025. PM was supported by the European Commission (Horizon 2020) as a Marie Skłodowska-Curie fellow under grant 660458; NPTJ was supported by the Gerrit Jan van Ingen Schenau Promising Young Scientist Award.

CONFLICT OF INTEREST

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Literature search.

Table S1: Summary of patient characteristics and reported data.

Table S2: Volume in white matter tracts and white matter regions, per CP subtype.

Table S3: Symmetry in white matter tracts, per CP subtype.

Table S4: Analysis of mean diffusivity, axial diffusivity, and radial diffusivity in addition to fractional anisotropy for corticospinal tract.

Figure S1: Flow chart of study inclusion.

How to cite this article: Jacobs NPT, Pouwels PJW, van der Krogt MM, Meyns P, Zhu K, Nelissen L, et al. Brain structural and functional connectivity and network organization in cerebral palsy: A scoping review. Dev Med Child Neurol. 2023;00:1–17. https://doi.org/10.1111/dmcn.15516