Neural correlates of visuomotor functions in preterm children: a literature review focused on unilateral Cerebral Palsy

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Abstract

Cerebral Palsy (CP) is the most common developmental disorder in preterm infants with spastic CP as the most prevalent motor type. Several aspects of visual perception and visuomotor control remain unsolved in children with spastic unilateral Cerebral Palsy (uCP). This is remarkable since CP is recognized as the leading cause of childhood motor disability, and comorbidities, such as visual problems, are well recognized in this condition. The co-occurrence of visual and motor impairments is related to the fact that the lesions to motor pathways are anatomically close to visual pathways in children with uCP. Previous studies attempted to define the relationship between visual disorders and brain damage in uCP, finding no specific correlation between the type and timing of the lesions and visual functions. Furthermore, research investigating which brain regions and tracts are responsible for specific visual functions and deficits is limited. The present review, therefore, aims to describe neurological correlates (i.e., structural MRI and diffusion MRI) of visuomotor deficits in children with uCP to identify the gaps in the current literature which could be addressed in future studies.

Keywords

Cerebral Palsy, Visual perception, Visuomotor control, Neuroimaging, Diffusion MRI

1. Introduction

Preterm birth, defined as birth before 37 completed weeks of gestation [1], can result in long term developmental impairments due to brain immaturity or damage occurring during the prenatal or perinatal period. The main disorders associated with prematurity are intellectual disability, hearing loss, visual impairment, and cerebral palsy [2].

Visual impairments refer to any degree of impairment to a person's ability to see, that affects his or her daily life [3]. For years, retinopathy of prematurity (ROP) was considered the most common cause of visual loss in infants with low birth weight [4]. ROP is an eye disorder caused by abnormal blood vessel growth in the light-sensitive part of the retina. However, recent studies [5] have shown that cerebral visual impairment (CVI) has replaced ROP as the main cause of visual disability in ex-preterm children [6]. CVI refers to a heterogeneous group of visual dysfunctions which *"cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment"* [7]. It includes disorders of basic visual functions such as acuity and stereopsis, but also higher visual dysfunctions of visual attention, depth and motion perception, object recognition and spatial cognition [8, 9]. A gestational age of less than 26 weeks is the most important factor associated with CVI (5.21%) [10, 2].

Cerebral Palsy (CP) is the most common developmental disorder in preterm infants. According to the literature, over 50% of children with CP are born preterm [11]. The prevalence of CP increases with decreasing gestational age at delivery [12]. In a meta-analysis, the pooled prevalence of CP in preterm infants is estimated to be 6.8% [13]. However, in extremely preterm born children (i.e. born before 28 weeks of gestation), the prevalence of CP increases up to 10%. CP is defined as a non-progressive permanent disorder of movement and posture due to disturbances in the developing fetal and infant brain [14]. In addition to impairments of gross and fine motor function (i.e., muscle tone, posture, and movement), CP manifests with deficits in sensory modalities such as visual function [14]. CVI in particular is reported in over half of children with CP [15, 16]. The presence of such impairments can have an important impact on planning and performing movements, due to a lack of information about the position of the hands as well as the target [17, 18]. As a consequence, visuo-motor integration and motor coordination skills might be hampered in children with CP not only due to their motor impairment.

CP also is a heterogeneous disorder and can be classified by its motor type and distribution. According to the Surveillance of Cerebral Palsy in Europe (SCPE) the motor type can be described as spastic, dyskinetic, ataxic, or mixed pattern [19], and the distribution of limb involvement as unilateral or bilateral. Spastic CP, characterized by pyramidal signs (i.e., spasticity, weakness), increased muscle tone, and joint stiffness, is the prevailing type [20], and the most common one in preterm infants or those with low birth weight [2]. Spastic CP can be further classified into unilateral CP (uCP), if only one side of the body is affected, and bilateral CP, if both sides are involved [21]. Children with uCP, who make up 30% of the total cases of CP [22], are often physically less impaired than those with bilateral CP, showing a higher degree of impairment in the upper limb in comparison to the lower limbs. Such impairments result from an injury predominantly lateralized to one brain hemisphere [23] which leads to a lower degree of deficits when compared to bilateral CP. Up to now, the majority of studies on children with uCP have been focusing on motor control [24] describing an irregular movement pattern of the impaired arm and difficulties with performing bimanual tasks [25]. On the contrary, visual impairments, also common in uCP [26, 15], have been less well investigated despite their impact on guiding and planning motor actions. As a result, several aspects of

visual perception and visuomotor control remain unsolved in children with uCP.

The present review, therefore, aims to summarize the current knowledge about visuo-motor deficits in children with uCP and identify the gaps in the current literature to be addressed in future studies. In Section 2, we describe the anatomy and functions of the visuomotor system and the related impairments in children with uCP. Section 3 highlights the findings on structural and diffusion neuroimaging in children with CP, focusing first on those related to motor function and secondly on those related to visual and visuomotor function. Lastly, Section 4 provides a summary of the findings described in previous sections, highlighting the need of future research to address the link between neuroimaging and visual and visuomotor function in children with uCP.

2. Visuomotor network in children with uCP

2.1. Anatomy and functions

The visual network is highly complex with 40% of the brain serving visual functions [27]. Visual information from the retina reaches the posterior visual pathways through the optic nerves and the optic chiasm (i.e., optic tracts). The optic tracts are the first structures of the posterior visual pathways which transfer information together with the lateral geniculate nucleus (LGN), the pulvinar, the superior colliculus and the optic radiations to the primary visual cortex (V1) located in the occipital lobe [28]. Damage to the optic tract, LGN, or optic radiations leads to visual field defects, which can vary depending on the site of the lesion [28]. Extension of the damage to V1 results in acuity loss [28]. From V1, visual information is sent to the higher visual areas located in the parietal and temporal lobes, where higher order visual processing takes place [28].

Historically, CVI has been explained within the framework of two distinct and inter-acting systems, the dorsal and the ventral stream [29]. The former is responsible for motion and object's spatial location and damage to the dorsal stream results in impairments in visual guidance of movement and simultaneous perception [27]. The latter is involved in object identification and damage to the ventral stream results in difficulties with object and face recognition and orientation in the environment [30]. In the last decades, a growing body of evidence [31, 32] has proposed more refined functional and anatomical circuits for visuo-motor processing. According to Pisella et al. [32], in the visuomotor system we can identify three different streams:
(1) a dorso-dorsal pathway, including the dorsal part of the parietal and pre-motor cortices, for immediate visuo-motor control [33, 34]. Damage to the dorso-dorsal pathway can result in optic ataxia, a deficit of visuo-manual guidance.
(2) a ventral prefrontal pathway with connections from the ventral visual stream to pre-frontal areas for spatial or temporal control of action. Damage to the ventral prefrontal pathway results in visual agnosia, a deficit of visual recognition.
(3) a ventro-dorsal pathway, including the ventral part of the parietal lobe and the pre-motor and pre-frontal areas, for complex planning and programming with a more bilateral organisation

and a hemispheric lateralization. Damage to the ventro-dorsal pathway results in mirror apraxia, characterized by misreaching errors when the controlesional hand is guided to a visual goal through a mirror. Another common deficit is limb apraxia, a brain disease affecting the performance of skilled and learned object-related movements [35]. Moreover, spatial neglect, a syndrome affecting the left space in the domains of perception, representation and action can also occur when this pathway is damaged.

An illustration of the visual network is provided in Figure 1.
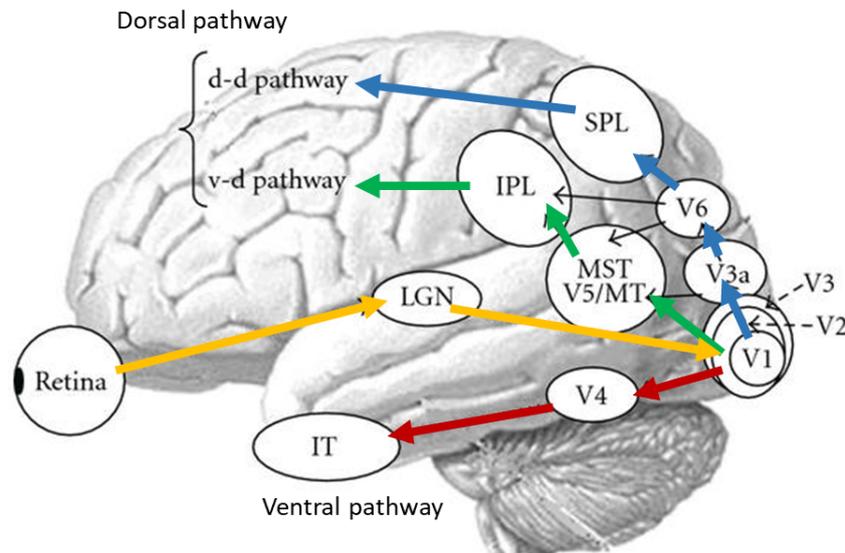
Figure 1: The visual network in humans. Dorso-dorsal pathway (d-d pathway) is shown in blue, ventrodorsal pathway (v-d pathway) in green, and the ventral pathway in red. In addition, the visual pathway from the retina to the primary visual cortex (V1) is highlighted in yellow. Lateral geniculate nucleus (LGN); secondary, tertiary, quaternary, and senary visual cortices (V2, 3, 4, and 6); accessory visual cortex (V3a, V3); quinary visual cortex/middle temporal area (V5/MT); medial superior temporal area (MST); inferior parietal lobule (IPL,); superior parietal lobule (SPL); inferior temporal cortex (IT). Figure adapted and modified from [36] with Open Access distributed under the Creative Commons Attribution License.

Overall, visual problems can be classified as peripheral or ocular (e.g., strabismus, refractive error, decreased acuity) if the damage occurs anterior to the optic chiasm and retrochiasmatic or cerebral when the damage occurs after the level of the optic chiasm [15]. Cerebral visual problems include visual perception (VP) and visuomotor integration impairments [30]. A full overview of visual functions is provided in Table 1 [37, 38, 15, 39].

Table 1

Overview of visual functions with the division in oculomotor [38], geniculostriate functions [37, 28], visual perceptual functions and visuomotor integration [15, 39].

Category	Name of function	Definition
Oculomotor functions	*Fixations*	Maintenance of the gaze on a single location or area
	Smooth Pursuit	Slower tracking movements of the eyes designed to keep a moving stimulus on the fovea
	Saccades	Rapid, ballistic movements of the eyes that abruptly change the point of fixation
Geniculostriate functions	*Visual acuity*	Ability of the eye to distinguish shapes and the details of objects at a given distance
	Visual field	Total area in which objects can be seen in the side (peripheral) vision as eyes are focused on a central point
	Contrast sensitivity	Ability to distinguish an object against its background
	Stereopsis	Perception of depth and three-dimensional structure through binocular vision
Visual perceptual (VP) functions	*Visual discrimination and matching*	Ability to detect features for processing the differences and similarities among visual stimuli
	Object recognition or visual closure	Ability to recognize an object when shown under an incomplete representation (i.e., noise on top of an image or missing parts)
	Visual spatial perception	Ability to determine spatial relations within and between objects, perceive depth, topographic orientation, and wayfinding
	Figure-ground perception	Ability to differentiate relevant object information from distracting background information
	Motion perception	Ability to understand a constantly changing visual environment
	Visual memory	Ability to integrate visual information with previous experience
Visuomotor integration	*Visually guided motor activity*	Reaching, locomotion
	Eye-hand coordination	Ability to coordinate the information received through the eyes to control the hands in the accomplishment of a given task

2.2. Visual and visuomotor impairments in children with unilateral cerebral palsy (uCP)

In children with CP, the prevalence of visual problems, including both ocular and cerebral impairments, varies between 40% and 50% while the prevalence of only CVI increases up to 70% [15, 16]. Several studies have attempted to describe high-level visual dysfunctions, however, these studies showed mixed results. Kozeis et al. [40] investigated visual perception in 105

children with spastic CP (aged 6–15 years), finding a reduced near visual acuity and abnormal or absent stereopsis. In addition, the scores on the Motor Free Visual Perception Test [41] used to assess visual discrimination, figure-ground perception, visual memory, visual closure, and visual spatial perception, were less than or equal to that of 6-year-old typically developing children. In a study of Fazzi et al. [15], different types of CP were found to be associated with different patterns of visual impairments. Furthermore, VP impairments seem to occur more frequently in children with spastic CP compared to other types of CP, in whom visuo-motor integration is more impaired than non-motor visual–perceptual skills [26, 42].

In the present paragraph, we specifically focus on results in children with uCP, starting with findings on oculomotor and geniculostriate functions, followed by higher-order visual deficits. A summary of the main studies on visual and visuomotor impairments in children with CP is reported in Table 2. According to the study of Fazzi et al. [42], children with uCP showed oculomotor impairment (e.g., altered smooth pursuit and saccades), a slight reduction in visual acuity and visual field, and altered stereopsis. With regard to higher-order visual functions, the systematic review of Auld [43] identified three assessments (i.e., Motor-Free Visual Perception Test [41]; Test of Visual Perceptual Skills [44, 45]; Developmental Test of Visual Perception [46]) for measuring high-level visual perception in children with uCP which showed good psychometric properties. Results from Burtner et al. [47] showed that children with uCP have significantly lower scores on the Motor-Free Visual Perceptual Test-Revised and on the Developmental Test of Visual Perception when compared to typically developing children. Specifically, only children with left hemiplegia scored significantly lower than typically developing children on the Motor-Free Visual Perceptual Test-Revised. These findings are in line with the recent study of Berelowitz and Franzsen [48], which investigated specific VP impairments in children aged 4-18 in South Africa, finding that left spastic uCP demonstrated consistently lower scores on all of the subtests of the Test of Visual Perceptual Skills and composite scores than those with right spastic uCP.

Additional studies [49, 50] report that children with uCP have deficits in sensorimotor integration and visuo-perceptual modalities, leading to difficulties in the execution of motor actions. Also, visual perceptual ability assessed by the Test of Visual Perceptual Skills, and unimanual capacity of the dominant upper limb evaluated by the Jebsen–Taylor Test of Hand Function, were found to be associated with activities of daily living process skills which were measured by Assessment of Motor and Process Skills) in children with uCP [51]. In addition, during object manipulation and reaching, children with uCP closely monitor the actions of the affected hand [52] by increasing the visual attention towards the impaired limb [53]. The increased attention could be explained as a compensation strategy for underlying visuomotor deficits [54] such as visual exploration and eye-hand coordination. Lastly, in the study of Surkar et al. [54], children with uCP showed impaired anticipatory visual control and eye-hand coordination which affects the planning of goal-directed actions. Hence, impairments in action execution are closely related to the ones in visuomotor coordination, suggesting important implications to take into account for diagnosis and rehabilitation of children with uCP.

Table 2

Studies on visual and visuomotor impairments in children with cerebral palsy.

Authors	N CP and age	CP	Main findings in visual and visuomotor functions
Kozeis et al., 2007 [40]	105 (range 6–15 yrs)	Spastic CP	Impairment in: · Visual acuity · Stereopsis · Visual discrimination · Figure-ground perception · Visual memory · Visual closure · Visual spatial perception
Fazzi et al., 2004 [42]	20 (range 5 – 8 yrs)	Spastic CP	Impairment in: · Visual acuity · Visual field · Stereopsis · Smooth pursuit · Saccades
Fazzi et al., 2012 [15]	17 (age not reported)	uCP	· Refractive errors · Strabismus Impairment in: · Visual field · Oculomotor behaviour
Burtner et al., 2006 [47]	20 (range 4-10 yrs)	uCP	· Impaired visual perception (i.e., Developmental Test of Visual Perception, Motor-Free Visual Perceptual, Test-Revised and School Function Assessment) · Left uCP lower scores on motor-free visual tests
Berelowitz and Franzsen., 2021 [48]	20 (range 5-18 yrs)	uCP	· Left uCP low scores on the test of Visual Perceptual Skills
Verrel et al., 2008 [52]	6 (range 14–19 yrs)	uCP	· Increased visual monitoring of impaired limb
Steenbergen et al.,1996 [53]	14 (range 15-20 yrs)	uCP	· Increased attention to impaired limb
Surkar et al., 2018 [54]	13 (mean age 6.8 + 2.9 yrs)	uCP	Impairment in: · Anticipatory visual control · Eye-hand coordination

CP, cerebral palsy; uCP, unilateral CP

3. Brain lesion in children with uCP

Visuomotor impairments result from brain damage that is highly heterogeneous in children with uCP.

Neuroimaging techniques allow the study of lesion extension and location which is needed to better understand and inform about the integrity of the different pathways responsible for visuomotor function. Among neuroimaging techniques, brain structural MRI (sMRI) and diffusion-weighted MRI (DWI) can provide high-resolution images of anatomy and white matter architecture of the cerebral structures of children with uCP [55].

3.1. Neuroimaging techniques

3.1.1. Structural MRI (sMRI)

Conventional MRI is used in hospital environments for the diagnosis and characterization of perinatal brain injury in pathologies such as CP and CVI [56, 57, 58]. With respect to CP, MRI sheds light on the location (e.g., lobe, hemisphere, structures), timing and extent of brain damage (i.e., cerebral hemispheres uni- or bilaterally). In the last decades, several classifications of MRI findings in CP have been proposed [31, 59, 60]. Below, we describe examples of qualitative and semi-quantitative interpretation of MRI data in children with CP.

Qualitative methods The MRI classification system (MRICS), developed by the Surveillance of Cerebral Palsy in Europe, SCPE [19, 59], defines the predominant neuroimaging pattern which most likely is the cause of the CP. MRICS is primarily a qualitative system including some simple quantitative aspects (e.g. uni- vs bilaterality, severity of a pattern such as basal ganglia/thalamus lesions). This classification has been found to be reliable based on the Reference and Training Manual and annual exchange and discussions among SCPE registered partners (i.e., clinicians dealing with CP, epidemiologists, and experts who work with CP registers from 18 countries). In the manual, which is available online with open access (https://eu-rd-platform.jrc.ec.europa.eu/scpe/reference-and-training-manual_en), brain abnormalities are classified into three major groups and subgroups. For a complete overview of the classification, see Table 3.

In a recent systematic review, Franki et al. [61] described the type of the underlying brain lesions in children with uCP. Taken together, approximately 5% of children with uCP had brain malformations. White matter lesions were the most common lesion type (57.8%) finding periventricular leukomalacia (PVL) in the majority of cases, followed by intraventricular haemorrhage (IVH) and the combination of PVL and IVH. Grey matter lesions were found in 14.8% of children with uCP while in 5% of these children, no visible lesions were found on sMRI.

Table 3
The harmonized classification of MRI, based on pathogenic patterns (MRI classification system) proposed by the SCPE network. Table adapted from [59].

Classification		Subclassification		Subtypes and/or examples
A	Maldevelopments	A1	Disorders of cortical formation	Disorders of proliferation
				Disorders of migration
				Disorders of organization
		A2	Other maldevelopments	Holoprosencephaly, Dandy Walker malformation, Corpus callosus agenesis, Cerebellar hypoplasia, etc.
B	White matter lesions	B1	Periventricular leukomalacia (PVL)	
		B2	Sequelae of intra-ventricular hemorrhage (IVH) or periventricular hemorrhagic infarction	
		B3	Combination of PVL and IVH sequelae	
C	Gray matter lesions	C1	Basal ganglia / thalamus lesions	Mild Moderate Severe
		C2	Cortico-subcortical lesions	
		C3	Arterial infarctions (middle cerebral artery or others)	
D	Miscellaneous			Cerebellar atrophy, cerebral atrophy, delayed myelination, ventriculomegaly not covered under B, hemorrhage not covered under B, brainstem lesions, calcifications, etc.
E	Normal			

Semi-Quantitative scale In the last years, a semi-quantitative scale (SQS) has been developed to describe the extent and location of lesions in MRI data of children with CP aged above 3 years old [62]. The SQS is structured in three main sections: (1) information on the technical characteristics of the scan and the type of lesion based on previous classification; (2) the graphical template for the brain hemispheres; (3) the scoring system for the hemispheres, subcortical structures (basal ganglia, thalamus, and brainstem), corpus callosum, and cerebellum. In section (2) of the SQS, lesions are traced onto a graphical black and white reproduction of six axial slices selected from the Montreal Neurological Institute (MNI) template. The scale makes a distinction between the cortical outline, the subcortical line separating the grey from the white matter, and a periventricular line bordering the periventricular white matter. Based on this subdivision, the brain template is made of three layers, namely a periventricular layer, a

middle white matter layer, and a cortico/subcortical layer. In section (3), hemispheric subscores include the number of affected slices; the number of affected lobes, the sum of the lobar scores for periventricular layer, the middle layer, and the cortico/subcortical layer. Right, left, and total scores are marked separately. Summary scores are calculated for the hemispheres, the basal ganglia and brainstem as total, right, and left scores, while for the corpus callosum and the cerebellum, scores are calculated as total scores only. The summary scores give a global score on the extent of a lesion, ranging from 0 to 40, with higher scores indicating more extensive lesions while information on topography is provided when subscores are considered. A detailed description of the methodology can be found in the study of Fiori et al. [62].

The reliability of the semi-quantitative scale was investigated in a study with 34 children with CP, among which 17 had uCP [62]. High interrater and intra-rater reliability of the total score was found with indices above 0.87 (kappa (k); intraclass correlation coefficients (ICC)). Nevertheless, a possible limitation of the semi-quantitative scale is that it uses the Montreal Neurological Institute template which is the international standard template for adults [63]. Indeed, to objectively analyse an MRI scan, it is necessary to compare the patient's MRI with an atlas built from the mean anatomical and physiological metrics as a function of disease and age [63]. Consequently, the use of age-specific brain atlases, built from averaging brain images of children in a specific age-range, is recommended [64]. Furthermore, the SQS scale [62] requires time investment in manual segmentation and anatomical knowledge of the examiner, which leads to its suboptimal application in population-based studies and in clinical practice. In the last decades, novel tools such as the use of automated volumetric segmentation, where the boundaries of a specific brain segment are measured automatically by a software program, have been developed. Pagnozzi et al. [65] developed an automated lesion segmentation pipeline for both white matter (WM) and grey matter (GM) lesions validated in 107 children with uCP. This tool showed positive correlations between lesions and clinical performance such as the Assisting Hand Assessment (AHA) which assesses the contribution of the impaired hand to bimanual activities [66] and the Test of Visual Perception Skills. Although the use of automated volumetric segmentation is not fully established in routine practice, such results highlight the important application of artificial intelligence techniques to optimize clinical research.

3.1.2. Diffusion MRI (dMRI)

Diffusion MRI (dMRI) provides insight into the microstructural development of the brain by measuring the random motion of water molecules [67]. In fibrous tissue, such as in the brain white matter (WM), water molecules tend to diffuse along the fibers, enabling the study of the orientation of the underlying structures. Different methods are used for measuring WM orientation, among which the most common are diffusion tensor imaging (DTI) and constrained spherical deconvolution (CSD) [68, 69].
DTI measures the three-dimensional diffusion of water as a function of spatial location [67]. In white matter, the presence of axons and bundles running in parallel constrains the free motion of water molecules, a condition known as diffusion anisotropy. This feature can be exploited to calculate different scalar measures namely fractional anisotropy (FA), mean diffusivity (MD),

radial diffusivity (RD), and axial diffusivity (AD) [67]. FA measures the degree of uniformity of water diffusion for a specific orientation [70]. Higher values are found in tissues with oriented structures organized in a common direction, such as white-matter tracts while lower values are found in damaged tissues due to the loss of coherence in the main diffusion direction. AD describes the diffusivity of water molecules parallel to fibers bundles while RD refers to the diffusivity of water molecules which is perpendicular to fibers bundles. Decreased AD but unchanged RD is typically assumed to indicate white matter damage. MD is a measure of the average diffusion in a certain time [71] and it is higher in damaged tissues as a result of increased free diffusion. The accuracy of the DTI model is limited in brain regions with crossing fibers where many voxels contain contributions from different oriented fiber populations and make it challenging to interpret metrics such as FA [72, 73]. To overcome this problem, one alternative method is constrained spherical deconvolution [68] which models the diffusion signal in each voxel as a function of all fiber orientations within the voxel (i.e., fiber orientation distribution - fOD). FOD can be used to calculate quantitative measures of microscopic and macroscopic white matter morphology (i.e., fiber density, fiber-bundle cross-section, fiber density and cross-section) and also to perform tractography [74, 68, 75, 76]. From both DTI and CSD metrics, it is possible to infer long-range connectivity patterns between distant brain regions namely Fibre Tractography (FT) [77, 78]. Fiber tractography is computed through algorithms that can be classified into deterministic [79] and probabilistic [80]. The former reconstructs the most likely trajectory from a given point (i.e., region of interest; ROI), the latter produces a distribution of trajectories, reflecting the degree of uncertainty of the trajectories.

As described above, dMRI has the potential application to describe the anatomic connections between different parts of the brain on an individual basis. This allows the possibility to investigate white matter tracts in a non-invasive way in clinical populations such as uCP.

3.2. Findings related to motor function

Diffusion MRI (dMRI) can provide a precise measures of structural connections of the brain. Over the past years, several studies applied dMRI to investigate structure-function relationships in children with uCP. The systematic review of Mailleux et al. [81] showed that in uCP, 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. In addition, in uCP white matter abnormalities were widespread across the brain including non-motor areas. In additional studies, lower FA (i.e., loss of coherence in the main diffusion direction due to tissue damage) and higher MD (i.e., increased free diffusion due to tissue damage) were found in the posterior limb of internal capsule (PLIC) and along the affected corticospinal tract (CST) [82, 83, 84], in thalamocortical projections, and fronto-parietal association pathways [84] of children with uCP when compared to the less affected hemisphere or the brain of typically developing children. Furthermore, tractography studies showed decreased white matter integrity in the CST, projections traversing the PLIC, thalamocortical projections, the medial lemniscus, the corpus callosum, and the corticopontocerebellar tracts of the lesioned hemisphere in children with uCP compared to the dominant hemisphere of typically developing children [85, 86, 87, 88, 83]. A summary of the main neuroimaging studies in children with uCP is provided in Table 4.

Table 4

Studies on neuroimaging in children with unilateral cerebral palsy (uCP).

Authors	N CP	MRI	Main findings
Pagnozzi et al., 2016 [65]	107 (mean age 10.9 yrs)	sMRI	· Lesion segmentation correlation to clinical outcomes
Mackey et al., 2014 [82]	20 (mean age 15 ± 3 yrs)	dMRI	· Lower FA, higher MD in the PLIC and in the affected CST
Weinstein et al., 2014 [83]	14 (mean age 10.6 ± 2.7 yrs)	dMRI	· Lower FA, higher MD in the PLIC and in the affected CST
Pannek et al., 2014 [84]	50 (range 5-17 yrs)	dMRI	· Low FA in CST, thalamocortical projections, and fronto-parietal association pathways
Fiori et al., 2015 [85]	36 (mean age 12.61 ± 3.2)	dMRI	· Disruption of structural cerebrocerebellar connectivitylinked to impaired hand function in bimanual skills
Hodge et al., 2017 [86]	28 (range 6-18 yrs)	dMRI	· Lower FA and RD associated with decreased size of CST and AHA and MA assessments
Kim et al., 2015 [87]	36 (mean age 5.6 ± 3.2 months)	dMRI	· Lower FA in CST associated with Functional Level of Hemiplegia scale
Kuczynski et al., 2017 [88]	29 (range 6-19 yrs)	dMRI	· Lower FA and higher MD, RD, and AD compared with the non-dominant hemisphere of controls · Impairments in proprioception correlated with lesioned hemisphere DCML tract
Kuczynski et al., 2018 [89]	33 (range 6-19 yrs)	dMRI	· FA, MD, RD, AD of lesioned CST correlated with visually guided reaching task performance
Weinstein et al., 2014 [83]	14 (mean age 10.6 ± 2.7 yrs)	dMRI	· Reduced WM integrity in CC, affected CST and affected PLIC related to hand function

CP, cerebral palsy; sMRI, structural MRI, dMRI, diffusion MRI; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity; PLIC, posterior limb of the internal capsule; CST, corticospinal tract; CC, corpus callosum; DCML, dorsal column-medial lemniscus; WM, white matter; AHA, assisting hand assessment; MA, Melbourne assessment

As highlighted in previous findings [81], most of the studies investigated the relationship between white matter integrity and motor function in children with uCP. Nevertheless, in children born very preterms dMRI findings (i.e., thalamic radiations, inferior longitudinal fasciculus, superior longitudinal fasciculus, inferior fronto-occipital fasciculus) also suggest the presence of white matter damage in brain regions not only involved in motor but also visual functions [90].

3.3. Findings related to visual and visuomotor function

Previous studies [91, 92, 93] have attempted to define a relationship between visual disorders and brain damage in children with CP. Results showed that PVL is the most common causative lesion in children with spastic CP and also frequently affects the visual pathways [94, 95, 96]. With regard to grey matter structures, damage to the thalamus has been associated with severe visual impairment [97, 98, 99, 100]; lesions to occipital-parietal areas with impairments in visual

crowding [101, 102], and reduction of the thickness of the primary visual cortex with motion perception in children with PVL [103]. The study of Tinelli et al. [96] explored the relationship between type and severity of brain lesion on sMRI and visual function in children with bilateral CP and PVL. Brain damage scores (i.e., global structural, hemispheric, and subcortical) were calculated with the semi-quantitative template of Fiori et al [62]. Visual functions were assessed with age-specific tests for fixation, smooth pursuit, saccades, nystagmus, visual acuity, visual field, stereopsis, and colour perception. For each test they provided a score of 0 if it was not compromised or 1 when there was an impairment. A visual total score was obtained from the sum of all of the items, ranging from 0 to 8. Results showed that brain lesion severity strongly correlated with visual function total score. Specifically, visual acuity, visual field, stereopsis, and colour were compromised when cortical damage was present, while fixation and saccades were affected in the presence of subcortical brain damage. Similarly, a study of Sakki et al. [9] investigated the association of brain lesions with visual function (i.e., visual acuity, visual fields, contrast sensitivity, stereopsis, visual perception, visuomotor integration) in children with VP impairments with and without CP. Results showed that approximately half of the participants had abnormalities in the frontal, temporal, or striatum areas, and approximately three quarters in the occipital or parietal areas. Cerebellar or brainstem abnormalities were present in less than a fifth of the participants. Nevertheless, no clear associations were found between regions or number of brain lesions and degree of visual acuity and contrast sensitivity. As reported by the authors, this result differs from the findings of Tinelli et al. [96] who showed that cortical and subcortical lesions strongly correlated with visual function total score. One possible explanation is that Tinelli et al. [96] used a single category of "visual dysfunction" including fixation, saccades, nystagmus, acuity, visual field, stereopsis, colour perception, whereas Sakki et al. [9] investigated acuity and contrast sensitivity separately from visuoperceptual functions. Furthermore, a previous study [92] showed that visual field defects were not always related to damage in the optic radiations or the visual cortex and the review of Philip et al. [30] reported a low correlation between MRI and different patterns of visuoperceptual deficits. Indeed, it is important to mention, that not all damage of the brain leading to visual deficits is visible on sMRI. For example, Guzzetta et al. [104] studied 26 school-aged preterm born children, among which only 13 had PVL with significant visible brain damage on structural MRI. However, all 26 children showed significantly lower perception of pure global motion relative to full-term controls, irrespective of the presence of brain damage visible on MRI [104]. The lack of association between visual skills and observed anatomical brain anomalies can be explained by the fact that conventional MRI techniques do not reveal all structural injuries within the visual pathways [99, 8]. For example, premature infants frequently suffer from diffuse white matter injury not easily detectable on anatomical images [105]. Therefore, the application of more advanced neuroimaging techniques such as dMRI can further enhance the understanding of the visuomotor system in children with uCP .

Changes in the structural and functional integrity of white matter pathways such as the optic radiations, detected by dMRI, were found to be associated with reduced visual acuity and visual perceptual dysfunctions [106, 107, 102, 108]. More specifically, abnormalities in the inferior longitudinal fasciculus have been implicated in object recognition difficulties in children with CVI [102], while abnormal white matter connections of the visual cortex to the

temporal lobe was found in individuals previously diagnosed with CVI (mean age = 17.36 years ± 3.03 SD) [108]. Furthermore, recent findings from Chandwani et al. [90] showed that CSD metrics in several white matter tracts of the visual pathways (i.e., the splenium of the corpus callosum, bilateral representations of the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and posterior thalamic radiations) were significantly associated with abnormal visual attention scores in very preterm infants at 3–4 months corrected age. Such results start to clarify that already at a young age the link between visual-behavioral scores and brain structures can be demonstrated. Hence, follow up of visual-behavioural outcome is crucial for determining possible biomarkers. A summary of the main studies linking neuroimaging to visual and visuomotor outcomes is provided in Table 5. Although these studies bring important insights in the relation between brain damage and visual function, this has not been specifically investigated in children with uCP.

Table 5
Studies linking neuroimaging to visual and visuomotor outcomes.

Authors	N CP	Diagnosis	MRI	Main findings
Fazzi et al., 2009 [91]	22 (range 6–15 yrs)	Preterm, PVL, spastic diplegia	sMRI	· Deficit in visual functions not related to parietal and temporal WM, or GM of area of visual associative functions
Van den Hout et al., 2004 [93]	7 (mean age 5 yrs)	Preterm, PVL	sMRI	· Lower peritrigonal WM volume · Gliosis and cortical damage associated with poorer visuo-perceptual skill
Lanzi et al., 1998 [95]	38 (range 20 m to 5 yrs)	Preterm, PVL	sMRI	· Lesions in optic radiations and calcarinecortex related to lower visual acuity
Tinelli et al., 2020 [96]	72 (mean age 3.2–14.4 yrs)	Bilateral CP and PVL	sMRI	· Impaired visual acuity, visual field, stereopsis and colour associated with cortical damage · Impaired fixation and saccades associated with subcortical brain damage
Cioni et al., 1996 [97]	80 (age not reported)	Neonatal encepha-lopathy	sMRI	· Visual acuity related to damage to visual cortex and optic radiations
Ortibus et al., 2009 [99]	70 (range 4 –20 yrs)	Preterm, CP	sMRI	· Perceptual visual impairment related to dorsal stream impairments
Ricci et al., 2006 [100]	12 (mean age 1 yr)	PVL	sMRI	· Thalami atrophy and abnormal optic radiations related to visual functions
Bhat et al., 2021 [103]	13 (mean age 11.2 ± 4.5 yrs)	Preterm, PVL spastic diplegia	sMRI	· V1 cortical thickness negatively correlated with motion coherence sensitivity
Sakki et al., 2022 [9]	28 (range 5 –15 yrs)	CVI	sMRI	· Main damage in the postgeniculate visual pathways and visual cortex · No relation between brain scores (i.e., Fiori scale) and acuity and contrast sensitivity
Guzzetta et al.,2009 [104]	26 (range 8.2–12.9 yrs)	Preterm, PVL	sMRI	· Low score on motion perception compared to controls · Ventral stream-related functions related to the presence of PVL
Bauer et al., 2014 [106]	2 (range 16 – 22 yrs)	CVI	dMRI	· Lower density of WM in inferior frontal-occipital fasciculus and superior and inferior longitudinal fasciculi
Ortibus et al., 2012 [102]	11 (range 3y5mo–13 yrs)	CVI	dMRI	· Lower FA in the inferior longitudinal fasciculus related to impaired object recognition
Pamir et al., 2021 [108]	12 (range 14 –24 yrs)	CVI	dMRI	· Higher RD within cortico-cortical but not thalamo-hMT+ connections
Chandwani et al., 2022 [90]	191 (3–4 m corrected age)	Very preterm	sMRI dMRI	· FDC of the left posterior thalamic radiations, left inferior longitudinal fasciculus, right superior longitudinal fasciculus, and left inferior fronto occipital fasciculus associated with visual attention scores

CP, cerebral palsy; PVL, periventricular leukomalacia; CVI, cerebral visual impairment; sMRI, structural MRI, dMRI, diffusion MRI; FA, fractional anisotropy; RD, radial diffusivity; FDC, fibre density and bundle cross-section; hMT+, human middle temporal complex; WM, white matter; GW, grey matter

4. Conclusion and gaps

In sum, children with uCP are not only affected by their motor impairment, but they also present with heterogeneous visual dysfunctions, that potentially further impact their already compromised manual function.

Whereas the motor part of the clinical picture of children with uCP has been extensively studied, the visual deficits have not been systematically mapped and certainly, the relation between brain damage and visual dysfunction and the interplay with visuomotor function remains to be elucidated.

Previous findings showed that children with uCP have impairments in oculomotor, geniculostriate functions, visual perceptual, and visuomotor functions. Neuroimaging findings revealed that PVL is the most common structural brain lesion in children with uCP. With regard to dMRI, findings are mainly focused on children with CVI, showing lesions in the optic radiations and inferior longitudinal fasciculus and on very preterm infants conditions. Hence, research investigating which brain regions and tracts are implicated in specific visual functions and deficits in children with uCP is limited.

To our knowledge, no previous work has systematically and comprehensively mapped the neurological correlates (i.e., sMRI and dMRI) of the visual and visuomotor dysfunction in children with CP. Since little is known about the relevance of non-motor pathways, further studies are needed to investigate the contribution of visual pathway to visuomotor function in children with uCP.

Acknowledgments

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