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Corticospinal tract wiring and brain lesion characteristics in unilateral cerebral palsy: determinants of upper limb motor and sensory function

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Abstract

Brain lesion characteristics (timing, location, and extent) and the type corticospinal tract (CST) wiring have been proposed as determinants of upper limb (UL) motor function in unilateral cerebral palsy (uCP), yet an investigation of the relative combined impact of these factors on both motor and sensory function is still lacking. Here, we first investigated whether structural brain lesion characteristics could predict the underlying CST wiring, and we explored the role of CST wiring and brain lesion characteristics to predict UL motor and sensory function in uCP.

Fifty-two participants with uCP (mean age (SD): 11y3m (3y10m)) underwent a single-pulse Transcranial Magnetic Stimulation session to determine CST wiring between the motor cortex and the more affected hand (n=17 contralateral; n=19 ipsilateral; n=16 bilateral) and an MRI to determine lesion timing (n=34 periventricular (PV) lesion; n=18 cortico-subcortical (CSC) lesion), location, and extent. Lesion location and extent were evaluated with a semi-quantitative scale. A standardized protocol included UL motor (grip strength, unimanual capacity, bimanual performance) and sensory measures.

A combination of lesion locations (damage to the PLIC and frontal lobe) significantly contributed to differentiate between the CST wiring groups, re-classifying the participants in their original group with 57% of accuracy. Motor and sensory function were influenced by each of the investigated neurological factors. However, in a multiple regression analysis, motor function was predicted by the type of CST wiring (more preserved in individuals with contralateral CST wiring ($p<0.01$)), lesion extent and damage to the basal ganglia and thalamus. Sensory function seemed to be best predicted by the combination of a large and later lesion, and an ipsilateral or bilateral CST wiring, which led to increased sensory deficits ($p<0.05$).

These novel insights contribute to a better understanding of the underlying pathophysiology of UL function and may be useful to delineate individualized treatment strategies.

Introduction

Upper limb (UL) function is commonly impaired in individuals with unilateral cerebral palsy (uCP), negatively impacting on daily life activities [1]. The large variability in the clinical presentation of UL function, but also in treatment response, has resulted in increasing interest in understanding the underlying neural mechanisms that determine UL function, and its contribution to further optimize therapy planning for the individual with uCP. A number of neurological factors have been put forward as potential predictors of UL function, i.e. the structural brain lesion characteristics (i.e. lesion timing, location, and extent) and the type of corticospinal tract (CST) wiring [2–6].

The timing of the lesion during gestation is closely related to the type of the damaged tissue, and can be classified into three categories: malformations (1^{st} and 2^{nd} trimester of pregnancy), periventricular lesion (PV, early 3^{rd} trimester), cortico-subcortical lesions (CSC, late 3^{rd} trimester and around birth) [7]. Previous studies investigating the impact of lesion timing on UL function have shown that individuals with a later lesion (i.e. CSC lesions) present with poorer UL motor and sensory function [2, 3, 5]. Besides lesion timing, lesion location and extent have shown to play an important role in determining UL function, whereby damage to the posterior limb of the internal capsule (PLIC) and the basal ganglia, and a larger lesion extent are related to worse UL motor and sensory function [2, 3] However, there is still large variability in UL function that remains unexplained based on these factors.

The unilateral brain damage in individuals with uCP can also result in a partial or complete reorganization of the CST towards the non-lesioned hemisphere [8]. This reorganization of the CST wiring is unique in uCP and refers to the efferent motor input to the affected hand. Researchers have identified three types of CST wiring, i.e. contralateral (CST_{contra}, the affected hand receives input from the crossed CST, originating in the lesioned hemisphere), ipsilateral (CST_{ipsi}, the affected hand receives input from the uncrossed CST, originating in the non-lesioned hemisphere) and bilateral (CST_{bilat}, the affected hand receives input from both the crossed and uncrossed CST, originating in the lesioned and non-lesioned hemisphere, respectively) [8, 9]. It has been suggested that the type of CST wiring is the main factor influencing UL function, whereby individuals with CST_{contra} present with more preserved UL function compared to the other groups [6, 10–13]. Nevertheless, assessing the underlying CST wiring with Transcranial Magnetic Stimulation (TMS) in young children might become challenging. Therefore, the identification of either behavioural or brain lesion features that relate to the underlying CST wiring could be useful to define tailor-made interventions in a clinical setting.

Whilst the role of lesion timing, location and extent has been well investigated [2, 3, 14], only a few studies examined the impact of the CST wiring on UL function, and they often have several limitations (i.e. small sample sizes, ordinal scoring of impairments, limited to motor deficits) [5, 10, 15]. Moreover, studies thus far focused on each factor independently, whereas only one study described the impact of the CST wiring and lesion timing on UL function in uCP [10], and only one study reports the impact of CST wiring and lesion extent in children with PV lesions [4]. Although the authors suggested the relevance of both lesion timing and type of CST wiring in predicting UL function, the small sample size, the lack of a standardized evaluation of motor function, and the merely descriptive nature of the study, hampered the possibility of drawing strong conclusions. Furthermore, it has been shown that an intact sensory function is essential to develop an adequate motor function in other neurological disorders (such as adult stroke) [16, 17]. Also in individuals with uCP, sensory and motor function are highly related [1], although the impact of the CST wiring on this relationship remains unknown.

In this study, we investigated the impact of CST wiring and structural brain lesion characteristics on UL motor and sensory function in a large group of individuals with uCP, using a systematic and comprehensive evaluation. Our first hypothesis is that the type of CST wiring pattern in unilateral CP can be predicted based on a linear combination of measures of lesion timing, location and extent. Second, we hypothesize that the combination of these predictors together with the CST wiring has a stronger predicting value for UL motor and sensory function than any of these factors alone. Last, we speculate that the relation between motor and sensory function is disrupted by the type of CST wiring.

Materials and Methods

Participants

Children and adolescents with uCP aged between 5-21 years old were recruited via the CP reference center of the University Hospitals Leuven between 2014 and 2017. They were excluded if they (1) received UL botulinum toxin injections six months prior to the assessment, (2) had UL surgery two years prior to the assessment and/or (3) had other neurological or genetic disorders. All individuals assented to participate, all parents signed the informed consent (participants younger than 18 years old), and participants older than 12 years also signed the informed consent, in accordance with the declaration of Helsinki. This study was approved by the Medical Ethical Committee of the University Hospital Leuven (S55555 and S56513).

Participants with contraindications for the MRI (e.g. metal implants) or the Transcranial Magnetic Stimulation (TMS; ventricular-peritoneal (VP) shunt, seizure two years prior to the study) did not undergo the respective assessment. All TMS measurements were conducted by two experienced physiotherapists (CSM and EJ) and UL function was evaluated by four experienced physiotherapists (LM, CSM, JH and EJ) at the Clinical Motion Analysis Laboratory of the University Hospitals Leuven (campus Pellenberg, Belgium).

Upper limb evaluation

Motor function

Grip strength, unimanual capacity and bimanual performance composed the motor evaluation. Maximum *grip strength* was assessed using the Jamar® hydraulic hand dynamometer (Sammons Preston, Rolyan, Bolingbrook, IL, USA). The less-affected hand was measured first and the mean of three maximum contractions was calculated per hand. The ratio between hands was used for further analyses to cancel out the effect of age (grip strength ratio = grip strength less-affected hand/grip strength affected hand, whereby a lower score (closer to 1) indicates a grip strength in the affected hand similar to that of the less-affected hand). *Unimanual capacity* was assessed with the Jebsen-Taylor hand function test (JTHFT). The JTHFT reliably measures movement speed during six unimanual tasks [18, 19]. Similar to other studies, we used a modified version for children and adolescents with uCP in which the writing task was removed, and the time to carry out each task was reduced from 3 to 2 minutes to avoid frustration [19, 20]. The time to perform every task was summed up and the ratio between hands was used for further analyses to cancel out the effect of age (JTHFT ratio = JTHFT affected hand/JTHFT less-affected hand, whereby a lower score (closer to 1) indicates movement speed in the affected hand similar to that of the less-affected hand). *Bimanual performance* was evaluated with the Assisting Hand Assessment (AHA), which assesses how effectively the affected hand is used in bimanual activities [21–23]. The spontaneous use is evaluated during a semi-structured play session with standardized toys requiring bimanual handling. Given the age range of the participants of this study, the School Kids AHA and the Ad-AHA were administered [22, 24]. The AHA was scored by certified raters (LM and CSM), using the 5.0 version which includes 20 items that are scored from 0 ('does not do') to 4 ('effective use'), resulting in a final score between 0-100 AHA units.

Sensory function

Sensory assessments comprised measures of exteroception (tactile sense), proprioception (movement sense), two-point discrimination (2PD, Aesthesiometer®) and stereognosis (tactile object identification), which have been shown to be reliable in this population [25]. Tactile and movement sense were classified as normal (score 2), impaired (score 1) or absent (score 0). 2PD was classified according to the width between the two points that the participants could discriminate: normal (0-4mm, score 2), or impaired (>4mm, score 1) [26]. Tactile object identification was used as the number of objects that the children could recognize (0-6). In addition, a kit of 20 nylon monofilaments (0.04g - 300g) (Jamar® Monofilaments, Sammons Preston, Rolyan, Bolingbrook, IL, USA) was used to reliably determine threshold values for touch sensation [27, 28]. Touch sensation was categorized as normal (0.008-0.07g), diminished light touch (0.16-0.4g), diminished protective sensation (0.6-2g), loss of protective sensation (4.19-180g) and untestable (300g), according to the manual (Jamar® Monofilaments, Sammons Preston, Rolyan, Bolingbrook, IL, USA).

Structural MRI

Structural images were acquired using three-dimensional fluid-attenuated inversion recovery (3D FLAIR) [321 slices, slice thickness = 1.2 mm, slice gap = 0.6 mm, repetition time = 4800 ms, echo time = 353 ms, field of view (FOV) = 250 x 250 mm², 1.1 x 1.1 x 0.56 mm³ voxel size, acquisition time = 5 minutes]. In addition, magnetization prepared rapid gradient echo (MPRAGE) was acquired [182 slices, slice thickness = 1.2 mm, slice gap = 0 mm, TR =

9.7ms, TE = 4.6ms, FOV = 250x250mm^2, voxel size = 0.98x0.98x1.2, acquisition time = 6 minutes]. The structural MRI was used to provide a detailed description of the lesion location and extent and to classify the timing of the lesion, which was conducted by a paediatric neurologist (EO).

Timing of the brain lesion was classified according to the predominant pattern of damage as described by Krägeloh-Mann and Horber (2007) [7]: malformations (1^{st} and 2^{nd} trimester of pregnancy), periventricular lesion (PV, early 3^{rd} trimester), cortico-subcortical lesions (CSC, late 3^{rd} trimester and term), or acquired brain lesions (between 28 days and two years postnatally).

Lesion location and extent was determined using a semi-quantitative scale recently developed by Fiori et al (2014) [29]. The scale consists of a graphical template with six axial slices of the brain, and an extra template for the basal ganglia (lenticular and caudate), thalamus, posterior limb of the internal capsule (PLIC), brainstem, corpus callosum, and cerebellum. Firstly, the slices corresponding to the template slices are to be found and the lesion is drawn onto the template. Next, the damage to the periventricular, middle and cortico-subcortical layers of each lobe are scored for both hemispheres separately. The sum of the damage to each lobe results in the lobar score, ranging from 0-3 for each lobe. Damage to the basal ganglia (lenticular and caudate), thalamus, PLIC, and brainstem directly is binarily scored from the MRI (affected or non-affected). Damage to the corpus callosum is scored from 0-3, based on the involvement of the anterior, middle and posterior thirds of the corpus callosum on a sagittal view. Last, the involvement of the cerebellum is based on damage to the vermis (0-1) and each of the hemispheres (0-2), resulting in a total score ranging from 0-3. A total ipsilesional score is calculated based on the damage to the lobes (0-3 for each lobe, i.e. total of 0-12) and damage to the subcortical structures (0-5; ranging from 0-17). More detailed information about the scale and its scoring procedure can be found in the respective study [29]. This semi-quantitative scale has been shown valid and reliable in children with uCP [29, 30].

In the present study, lesion **location** was indicated by the damage to the frontal and parietal lobes (0-4), damage to the basal ganglia and thalamus (0-3), and damage to the PLIC (0-1). These locations were chosen based on their relation to the sensorimotor system [31]. Lesion **extent** was indicated by the total ipsilesional score (0-17).

Transcranial Magnetic Stimulation

Single-pulse TMS was conducted to assess CST wiring. TMS was applied using a MagStim 200 Stimulator (Magstim Ltd, Whitland, Wales, UK) equipped with a focal 70mm figure-eight coil and a Bagnoli electromyography (EMG) system with two single differential surface electrodes (Delsys Inc, Natick, MA, USA). A Micro1401-3 acquisition unit and Spike software version 4.11 (Cambridge Electronic Design Limited, Cambridge, UK) were used to synchronize the TMS stimuli and the EMG data acquisition. Motor Evoked Potentials (MEPs) were bilaterally recorded from the muscles opponens pollicis brevis. During the TMS assessment, participants wore a cap that allows creating a grip with a coordinate system to identify the optimal point to stimulate (hotspot) in a standardized and systematic way. The hotspot and the resting motor threshold (RMT, defined as the minimum intensity required to obtain 5/10 MEP of at least 50μV in the corresponding muscle) were identified by starting the stimulation intensity at 30% with an incremental increase of 5% [4]. For each hemisphere, stimulation started from the assumed "motor hotspot", which is located 5cm lateral and 1cm anterior from the scalp middle point (Cz), at 30%. After approximately 2-3 pulses, the stimulation intensity was increased 5% for another 2-3 pulses, until MEPs were found. If no MEP can be elicited after increasing up to 60 to 80%, the coil would be moved to a different location on the scalp grid, and the procedure would be repeated until an MEP was elicited. Stimulation up to 100% of the maximum stimulator output was continued until an MEP was elicited. The non-lesioned hemisphere was always stimulated first and allowed to identify contralateral CST projections to the less-affected hand. Stimulation in the non-lesioned hemisphere was continued up to 100% of the maximum stimulator output to search for possible ipsilateral CST projections to the affected hand. Next, the lesioned hemisphere was stimulated to identify possible contralateral CST projections to the affected hand. If only contralateral MEPs from each hemisphere were found, the child was categorized as having a CST_{contra} wiring. If MEPs in the affected hand were evoked from both hemispheres, the child was categorized as having a CST_{bilat} wiring. Lastly, if MEPs in the impaired hand were only evoked when stimulating the non-affected hemisphere, the child was categorized as having a CST_{ipsi} wiring. TMS measures have been shown to be reliable in adults [32, 33] and in children [34]. In this study, the TMS assessment was used for diagnostic purposes. In cases when high intensities were not tolerated, the stimulation intensity was increased up to at least 80% of the maximum stimulator output and children were asked to hold a pen to ensure pre-contraction of the evaluated muscle, and thereby facilitate the CST and MEP detection. This allowed us to rule out the possibility of mis-categorizing the child regarding their CST wiring pattern.

Statistical analyses

First, descriptive statistics were used to document the distribution of brain lesion characteristics according to the CST wiring. Next, we investigated the differences in occurrence of lesion timing, location, and extent between the CST wiring groups by using analysis of contingency tables (Chi-Square and Fisher's exact test), Kruskal-Wallis test (ordinal data), and ANOVA (lesion extent). Lastly, we used discriminant analysis to explore whether the type of CST wiring would differ depending on the linear combination of lesion timing, location, and extent, in a multivariate way. Cross-validation procedure was included to investigate the accuracy of the model in reclassifying the participants in the original CST wiring groups. Variables related to lesion timing, lesion location (damage to the frontal lobe, parietal lobe, PLIC, and basal ganglia and thalamus), and extent (ipsilesional extent of the lesion) were included in the model, which was fitted using the stepwise selection method.

To investigate the impact of the type of CST wiring and brain lesion characteristics on UL function, we first used linear simple regression and then multiple regression analysis to investigate the combined impact of these factors on UL motor and sensory function. For the continuous variables related to motor function, normality was first verified by inspecting the histograms and with the Shapiro-Wilk test, showing a normal distribution only for the AHA. For the JTHFT ratio and the grip strength ratio, a logarithmic transformation was applied ($y' = \log10(y)$). To investigate the impact of the type of CST wiring and brain lesion characteristics on UL motor function, we computed a multiple regression analysis. Similarly, for UL sensory function, we conducted a simple ordinal logistic regression for stereognosis and thresholds for touch sensation, and a simple logistic regression for 2PD to investigate the impact of each individual neurological factor on the sensory function. Next, we performed multiple regression analyses (ordinal and logistic) to investigate the combined impact of the neurological predictors on the sensory deficits. The predictors included in the multiple regression model were the type of CST wiring, lesion timing, location (damage to the frontal lobe, parietal lobe, PLIC, and basal ganglia and thalamus), and ipsilesional extent of the lesion. To predict both motor and sensory function, interaction terms were built between the CST wiring and (i) lesion timing, and (ii) lesion extent, and included in the model. The multiple regression models were fitted with the backward elimination method until a set of variables significantly contributing to the model was identified.

Lastly, to investigate the relation between sensory and motor function for the whole group and within CST wiring groups, Spearman rank correlation coefficients were used between each of the motor function variables and deficits in stereognosis. Correlation coefficients were considered as little or no correlation (<0.30), low (0.30-0.50), moderate (0.50-0.70), high (0.70-0.90) and very high correlation (>0.90) [35].

In addition, effects sizes were calculated for the comparisons and interpreted according to Cohen, depending on the computed test: η^2 (partial etha squared) for the prediction models (small 0.01, medium 0.06, large 0.14) [36, 37]. Statistical significance was set at $\alpha<0.05$ for main tests with Bonferroni correction for post-hoc tests. All statistical analyses were computed with SPSS Statistics for Windows version 24.0 (IBM Corp. Armonk, NY: IBM Corp.).

Results

Participants

Seventy-five children and adolescents with uCP participated in this study (mean age (SD): 11y1m (3y6m); 33 girls; 39 left uCP). According to the Manual Ability Classification System (MACS), 25 individuals were classifed as MACS I, 25 as MACS II and 25 as MACS III. Sixteen participants did not have CST wiring data (n=1 panic attack, n=2 hemispherectomy, n=3 VP shunt, n=2 epilepsy, n=1 tumor, n=4 refusals to participate, n=3 inconclusive TMS results), resulting in a total of 59 participants. The TMS assessment identified 20 individuals with CST_{contra}, 18 with CST_{bilat} and 21 with CST_{ipsi}. For the analyses in this study, participants with malformations (n=1), acquired lesions (n=4) or no visible lesions (n=2) were excluded due to the very small sample size of these sub-groups, resulting in a total group of 52 participants (mean age (SD): 11y4m (3y10m); 22 girls; 28 left uCP) with available CST wiring (n=17 contralateral; n=19 ipsilateral; n=16 bilateral) and data related to the timing, location, and extent of the lesion. A summary of the lesion locations and extent according to the lesion timing is provided in Supplementary materials (Table 1). Thirty-four individuals had a PV lesion and 18 had a CSC lesion. Clinical motor and sensory data was missing in one participant (boy, 19y7m, PV lesion, and CST_{contra} wiring) and sensory data was evaluated in a subsample of participants (see sensory function results section for more details).

CST wiring and brain lesion characteristics

Table 1 displays the distribution of lesion timing, location and extent variables according to the three CST wiring groups. Except for the damage to the parietal lobe, all variables were significantly different between the CST wiring groups ($p<0.05$) (Table 1).

In the discriminant analysis, we found that the combined value of the damage to the PLIC and the damage to the frontal lobe could significantly discriminate between the type of CST wiring (Wilks' $\lambda = 0.611$, Chi-square = 23.88, df = 4, Canonical correlation = 0.602, $p < 0.001$). The two functions extracted accounted for nearly 57% of the variance in the type of CST wiring. The standardized discriminant function coefficients of the two extracted functions indicated the contribution of each retained independent variable (damage to the PLIC and damage to the frontal lobe) to each function, showing how strongly the discriminant variables affect the score. These coefficients can be then used for the classification of a single individual (Function 1 = 0.81*damage to the PLIC + 0.50*damage to the frontal lobe; Function 2 = -0.60*damage to the PLIC + 0.88*damage to the frontal lobe).

Table 1. Contingency table (count and percentage, descriptive statistics) of the occurrence of lesion timing, location, and extent according to the CST wiring.

			CST wiring			
			Contralateral	**Bilateral**	**Ipsilateral**	**p-value**
Timing						
Lesion timing[¥]	PV	N (%)	15 (88.2%)	8 (50%)	11 (57.9%)	0.04
	CSC		2 (11.8)	8 (50%)	8 (42.1%)	
Location						
PLIC[¥]	Not affected	N (%)	8 (47%)	1 (6%)	0 (0%)	<0.001
	Affected		9 (53%)	15 (94%)	19 (100%)	
Basal ganglia and thalamus[◊]		Me (p25-p75)	0 (0-1)	1.50 (0 (2.50)	1 (1-2)	0.006 [a,b]
Frontal Lobe[◊]		Me (p25-p75)	1 (1-1)	1.50 (1-2.25)	1 (1-1.50)	0.004 [a,b]
Parietal Lobe[◊]		Me (p25-p75)	2 (1-2)	2 (1.25-3)	2 (2-2.50)	0.09
Extent						
Ipsilesional extent[○]		X (SD)	5.18 (3.07)	8.38 (3.95)	9.05 (3.27)	0.004 [a,b]

CST, corticospinal tract; PV, periventricular; CSC, cortico-subcortical; PLIC, posterior limb of the internal capsule. [¥]Chi-Square statistic, [§]Fisher's exact test, [◊]Kruskal-Wallis test, [○]ANOVA. [a] Contralateral vs. Ipsilateral; [b] Contralateral vs. Bilateral.

Cross-validated reclassification of cases based on the new canonical variables was successful in 57.7% of the cases: 89.5% were correctly classified in the CST_{ipsi} group, 47.1% in the CST_{contra} group, and only 31.3% in the CST_{bilat} group (Fig 1).

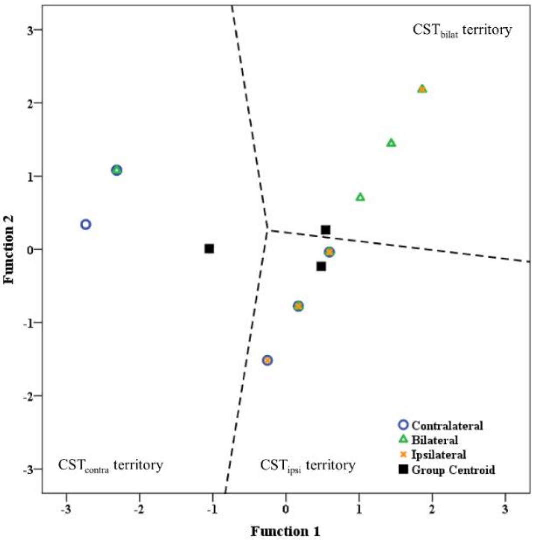

Fig 1. Territorial map showing the relative location of the boundaries of each CST wiring category and the location of each of the participants. The group centroids are indicated with a black filled square [CST_{contra} (-1.05, 0.01); CST_{ipsi} (0.48, -0.23); CST_{bilat} (0.54, 0.26)].

CST wiring, brain lesion characteristics and UL function

Motor function

Descriptive statistics of the motor function according to the type of CST wiring, lesion timing, location, and extent are presented in Supplementary materials (Table 2). The simple linear regression analyses to predict motor function based on a single neurological factor showed that every factor had an influence on motor function (grip strength, $p<0.04$; JTHFT, $p<0.004$; AHA, $p<0.01$; see Supplementary materials Table 2 for detailed information).

When all the neurological factors were included in the same model in a multiple regression analysis, the backward elimination method identified the variables that were significantly contributing to the model. Table 2 documents the estimated marginal means, which represent the mean response in each CST wiring group adjusted by the covariates that significantly contribute to the model. The multiple regression model to predict **grip strength** deficits only retained the type of CST wiring, explaining 46% of the variance ($F(2, 51)=20.90$; $p<0.001$; $\eta^2=0.47$). For the **JTHFT**, 54% of the variance was explained by the type of CST wiring ($F(2, 51)=12.20$; $p<0.0001$; $\eta^2=0.34$, $R^2=46\%$) and the total extent of the lesion (F(1, 51)=8.05; p=0.007; η^2=0.15, ΔR^2=8%). For **bimanual performance** (AHA), the regression model explained 61% of the variance, with the type of CST wiring (F(2, 51)=19.03; p<0.0001; η^2=0.45, ΔR^2=52%), the total extent of the lesion (F(1, 51)=10.65; p<0.001; η^2=0.19, ΔR^2=5%), and the damage to the basal ganglia and thalamus (F(1, 51)=4.90; p=0.03; η^2=0.10, ΔR^2=4%) significantly contributing to the model (Fig 2). No interaction effects were identified for any of the motor outcome variables.

Table 2. Descriptive statistics of the observed and estimated marginal means of upper limb motor function according to the CST wiring groups.

	Estimated marginal means and SD		
	CST_{contra} (n=16)	**CST_{ipsi} (n=19)**	**CST_{bilat} (n=16)**
Grip strength ratio (log)	0.14 (0.13)[a]	0.55 (0.20)[a]	0.46 (0.24)[a]
JTHFT ratio (log)	0.30 (0.24)[b]	0.67 (0.23)[b]	0.64 (0.22)[b]
AHA (0-100)	79.66 (10.28)[c]	58.70 (9.81)[c]	61.58 (9.67)[c]

CST, corticospinal tract; JTHFT, Jebsen-Taylor Hand Function test; AHA, Assisting Hand Assessment; SD, standard deviation. [a] The values coincide with the observed values, as there is not significant covariate in the model. [b] Adjustments based on ipsilesional lesion extent mean = 7.67. [c] Adjustments based on ipsilesional lesion extent mean = 7.67, and damage to the basal ganglia and thalamus mean = 1.12.

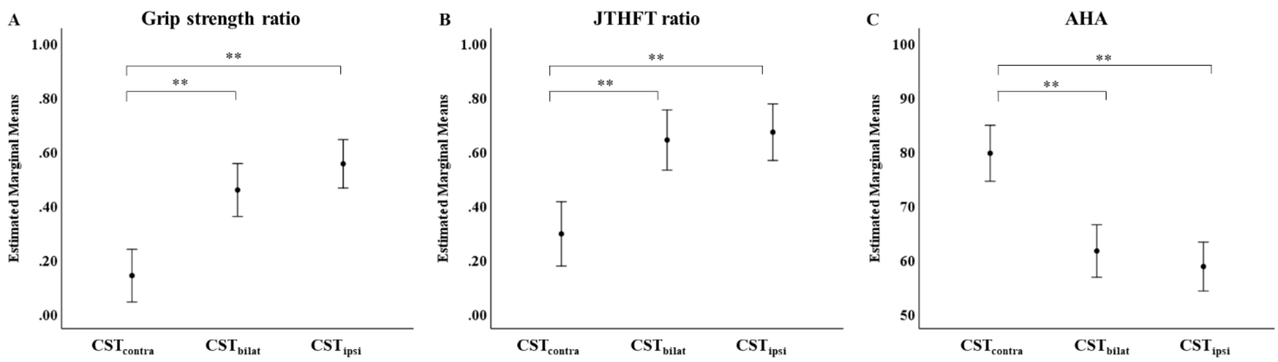

Fig 2. Upper limb motor function differs in individuals with CST_{contra} compared to those with CST_{bilat} or CST_{ipsi} wiring. Estimated Marginal Means and 95% CI per CST wiring type and lesion timing group for A) Grip strength (log ratio, i.e. closer to zero indicates preserved grip strength), B) JTHFT (log ratio, i.e. closer to zero indicates preserved manual dexterity, measured by speed) and C) AHA.
AHA, Assisting Hand Assessment; JTHFT, Jebsen Taylor Hand Function Test; CST, corticospinal tract. *p<0.01; **p<0.001. Estimated Marginal Means are adjusted according to the significant covariates (see Table 2 for details).

Sensory function

Descriptive information of sensory function according to each neurological factor is summarized in Table 3 of Supplementary materials. Sensory function data (tactile sense, movement sense, stereognosis and 2PD) and thresholds for touch sensation, as assessed with the monofilaments, were available in 46 and 35 individuals, respectively. Due to the lack of variation in the tactile sense and movement sense modalities, the predictive model was only applied to the stereognosis, 2PD and the thresholds for touch sensation.

The simple linear analyses to predict sensory function based on a single neurological predictor indicated that every predictor impacted on stereognosis ($p<0.032$). In contrast, 2PD was influenced by all neurological predictors ($p<0.04$) except the damage to the PLIC ($p<0.17$), and touch sensation could be significantly predicted by all factors ($p<0.01$) except damage to the PLIC ($p=0.99$) and type of CST wiring ($p=0.42$).

When all the neurological factors were included in the same model in a multiple regression analysis, the backward elimination method identified predictors that were significantly contributing to the model. For **stereognosis**, the retained main effects were the CST wiring (Wald Chi-square (2) = 9.09, $p=0.011$), lesion timing (Wald Chi-square (1) = 4.34, $p=0.04$) and ipsilesional extent of the lesion (Wald Chi-square (1) = 7.15, $p=0.008$) (Table 3A). These results show that the odds of having better stereognosis function were 5.56 times higher in the group with PV lesions than in the CSC group ($p=0.04$). Similarly, individuals with a CST_{contra} wiring show 10.23 and 9.7 times higher probability of having better scores in the stereognosis test compared to those with a CST_{ipsi} or CST_{bilat}, respectively ($p=0.02$), whilst there was no difference between the last two ($p=0.34$). Lastly, the odds of having higher stereognosis scores decreases by 0.74 for every unit change in the ipsilesional extent of the lesion ($p=0.01$). No interactions were found between the CST wiring and the brain lesion characteristics to predict deficits in stereognosis ($p>0.05$)

The logistic multiple regression to predict **2PD** showed lesion timing (Wald Chi-square (1) = 10.62, $p=0.001$) and ipsilesional extent of the lesion (Wald Chi-square (1) = 3.75, $p = 0.05$) to be significant contributors ($p>0.05$) (Table 3B). The odds of having an impaired 2PD is 31 times higher in the group with CSC lesions than in the PVL group ($p=0.001$). Secondly, the odds of having impaired 2PD increase by 1.34 for every unit change in the ipsilesional extent of the lesion (p=0.05). No interactions were found between the CST wiring and the brain lesion characteristics to predict deficits in 2PD (p>0.05)

Table 3. Descriptive statistics of the sensory function (3A, stereognosis (number of correctly recognized objects; 3B, two-point discrimination; 3C, touch sensation) according to each of the variables significantly contributing to each prediction model.

Table 3A

		Stereognosis (number of correctly guessed objects)						
		0	**1**	**2**	**3**	**4**	**5**	**6**
Lesion timing								
PV	N (%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	5 (71%)	6 (67%)	17 (44%)
CSC	N (%)	5 (100%)	2 (100%)	3 (75%)	1 (100%)	2 (29%)	3 (33%)	1 (6%)
CST wiring								
Contralateral	N (%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)	1 (11%)	13 (72%)
Bilateral	N (%)	4 (80%)	0 (0%)	2 (50%)	0 (0%)	3 (43%)	3 (33%)	3 (17%)
Ipsilateral	N (%)	1 (20%)	2 (100%)	1 (25%)	1 (100%)	4 (57%)	5 (56%)	2 (11%)
Lesion extent								
Ipsilesional	Me (IQR)	13 (2.07)	13 (-)	10 (3.88)	-	6 (3.50)	6 (5.25)	5.25 (3.75)

Table 3B

		Two-point discrimination	
		Normal (≤4mm)	**Impaired (>5mm)**
Lesion timing			
PV	N (%)	26 (93%)	3 (17%)
CSC	N (%)	2 (7%)	15 (83%)
Lesion extent			
Ipsilesional	Me (IQR)	5.25 (3.88)	12 (5.25)

Table 3C

		Threshold of touch sensation				
		Normal	**Diminished light touch**	**Diminished protective sensation**	**Loss of protective sensation**	**Untestable**
Lesion extent						
Ipsilesional	Me (IQR)	6 (4.50)	-	10.50 (11.25)	13 (2.41)	12.50 (-)

PV, periventricular lesion; CSC, cortico-subcortical lesion; CST, corticospinal tract; N, number of cases; Me, median; IQR, interquartile range.

The ordinal logistic multiple regression for **touch sensation**, as measured by the monofilaments, indicated that only the lesion extent significantly contributed to the deficits in touch sensation (Wald Chi-square (1) = 10.75, p=0.001) (Table 3C). The odds of having better touch sensation decreases by 0.66 for every unit change in the ipsilesional extent of the lesion. No interactions were found between the CST wiring and the brain lesion characteristics to predict deficits in touch sensation (p>0.05).

Impact of CST wiring on the relation between motor and sensory function

The correlation analyses between the motor and sensory function for the whole group indicated a moderate association between the stereognosis score and grip strength ratio (r_s = -0.60, p<0.001), JTHFT ratio (r_s = -0.60, p<0.001) and AHA (r_s = 0.61, p<0.001).

After group division according to CST wiring, there was no to low correlation between motor function and stereognosis in the CST_{contra} and CST_{ipsi} groups (r_s (range) = -031-0.36, p>0.05). Interestingly, in the CST_{bilat} group, moderate correlations were found with the JTHFT ratio (r_s= -0.48, p=0.07) and the AHA (r_s=0.65, p<0.01), despite a low correlation with grip strength ratio (r_s = -0.31, p=0.2). An illustration of the individual data points regarding these results can be found in Fig. 3.

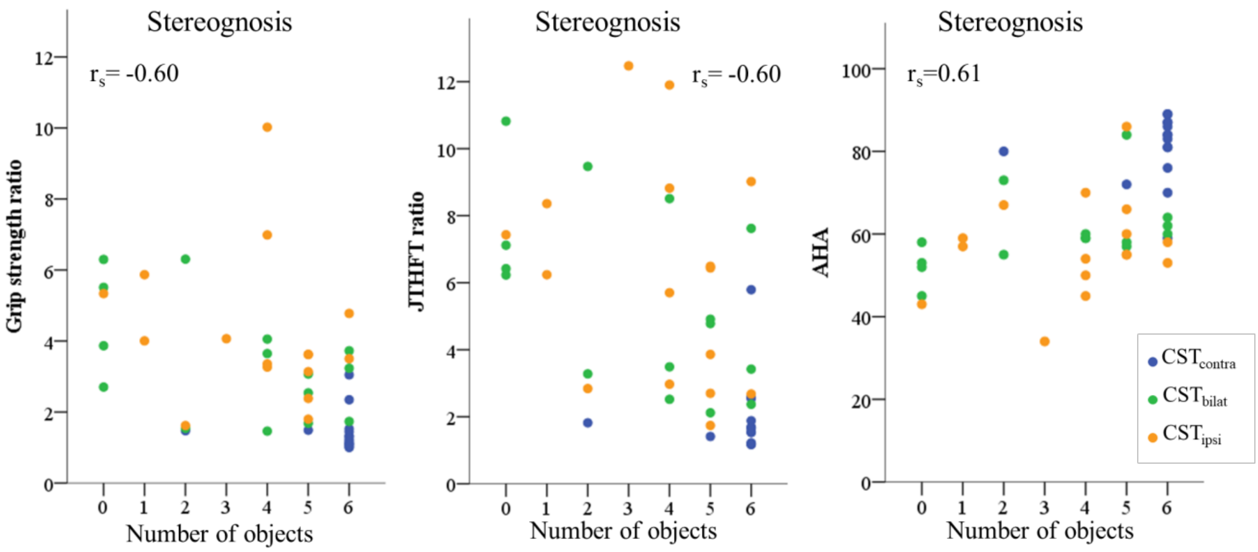

Fig 3. The relation between motor and sensory function seem to vary depending on the CST wiring. Individuals with a CST_{contra} and CST_{ipsi} showed no to low correlations, whereas those with CST_{bilat} showed moderate correlations. Each dot represents an individual child, with CST_{contra} (blue), CST_{bilat} (green), and CST_{ipsi} (orange). Correlations between stereognosis

with grip strength ratio (ratio, i.e. closer to one indicates preserved grip strength), JTHFT ratio (ratio, i.e. closer to one indicates preserved grip strength), and AHA. Correlation coefficients correspond to the analysis for the whole group.

Discussion

In this study, we explored the predictive value of brain lesion characteristics on the type of CST wiring as well as the impact of these factors on UL motor and sensory function. A comprehensive and standardized evaluation of both motor (grip strength, unimanual capacity and bimanual performance) and sensory function was used to predict UL function in a large cohort of individuals with uCP.

Our first research question examined the discriminant ability of lesion timing, location and extent to predict the type of CST wiring. A simple linear analysis demonstrated that lesion timing, location and extent were significantly different between the CST wiring groups. Our results showed that a CST_{contra} was only seen in 2 out of 18 children with a CSC lesion, compared to 15 out of 34 children with a PV lesion. Current results suggest that damage to cortical and/or subcortical structures (i.e. CSC lesion), reduces the potential of the CST to develop according to its typical contralateral trajectory. We hypothesise that this is likely driven by the reduced neural activity in the motor cortical areas after a CSC lesion, which are crucial for the development of the CST during the postnatal period [38]. However, a contralateral development of the CST is still possible in CSC lesions, and it may occur differently depending on lesion location and extent.

Once all predictors were simultaneously entered in a multiple linear analysis, we found that the combination of the damage to the PLIC and the frontal lobe significantly discriminated between the CST wiring groups. Half of the children in the CST_{contra} group showed damage to the PLIC, in contrast to the 94% and 100% in the CST_{bilat} and CST_{ipsi} group who showed damage to this white matter bundle. Furthermore, the frontal lobe was also more damaged in the CST_{bilat} and CST_{ipsi} groups, compared to the CST_{contra}. Although it is not unexpected that the PLIC and the frontal lobe are the two significant predictors in the model, due to their undoubtable relation with the motor cortex and the performance of actions, this is the first time that this interaction with the type of CST wiring is shown. Contrary to the importance of the location, Staudt et al (2002) postulated that the type of CST wiring depended on the lesion extent [4]. However, as they only included children with a PV lesion, their results cannot be extended to all the uCP population. Further efforts should be made to underpin whether structural damage of the brain lesion may serve as a biomarker of the underlying CST wiring.

Next to the predictive model, we also investigated how accurate the two functions derived from the discriminant analysis would be to reclassify the individuals in their original categories. Despite the significant contribution of the PLIC and the frontal lobe to the discriminant model, the classification accuracy only reached 57%, suggesting that timing, location and extent of the lesion (as included in the model) do not provide sufficient accurate information to predict the underlying type of CST wiring. Notwithstanding the validity and reliability of the semi-quantitative scale that was used to investigate lesion location and extent, we acknowledge that the semi-quantitative character of the scale may have underestimated the predictive value of the structural brain damage. Therefore, these results should be replicated in the future with volumetric measures of the different brain structures. For example, the projections to the PLIC have been shown to be topographically organized with reduced microstructural integrity in children with uCP [39] by using diffusion measures. Investigating the volumetric damage to the frontal lobe and the microstructural integrity of the PLIC may provide with further insights in determining the type of CST wiring in uCP.

For our second research question, we investigated the impact of CST wiring and brain lesion characteristics (timing, location, and extent) on motor and sensory function. Regarding ***motor outcome***, simple linear regression analyses indicated that the CST wiring and all brain lesion characteristics had an influence on the grip strength, manual dexterity and bimanual performance, which confirmed what previous studies have shown [5, 6, 10]. However, in the multiple linear regression analysis, we found that the underlying CST wiring plays a major, but not unique, role in determining UL motor function, as lesion location and extent also significantly contributed to increasing the explained variance for the JTHFT and for the AHA. Specifically, the type of CST wiring explained 46% and 52% of the JTHFT and the AHA variances, respectively, which was increased up to 54% and 61% by including lesion extent and damage to the basal ganglia and thalamus into the model. In general, our results show that a CST_{ipsi} or CST_{bilat} lead to poorer UL motor function compared to CST_{contra} for all motor outcomes, even when controlling for the significant contribution of lesion extent and location. The importance of the underlying CST wiring is an expected result, as the CST is the main motor drive and its damage causes vast disturbances on voluntary motor control, drastically reducing motor capabilities [38]. Whilst lesion timing, location, and extent have been put forward as a predictor of UL function [2, 3] and was also confirmed in our linear regression analysis, the huge variability in motor function reported by previous studies seems to be mainly explained by the underlying CST wiring. Staudt et al. (2004) were the first to report on the relation between CST reorganization potential at different gestational ages and UL motor function [10]. These authors also found that, along with the CST wiring, UL motor function further worsened in later lesions (CSC lesions) [10]. Linear regression analysis also showed that later lesions led to poor motor outcome, but multiple regression analysis revealed that lesion location and extent were key factors, next to the type of CST wiring. Although later lesions seem to be associated to a larger extent [3], it seems that the lesion extent itself plays a more important role in motor outcome, i.e. children with a PV lesion with large extent will also present with poorer hand function. Interestingly, the damage to the basal ganglia and thalamus explained an extra 4% of the variability in the AHA. In accordance with our results, previous studies have reported the negative impact of these subcortical structures on UL motor outcome [2, 5].

It is important to note that we still found large variability in the three motor outcome measures within both the CST_{ipsi} and CST_{bilat} groups, whereas the variability in the CST_{contra} group was rather small (Fig 2, see also Table 2 Supplementary materials for observed means). In other words, some individuals with a CST_{ipsi} and CST_{bilat} had good motor function, similar to those with a CST_{contra} wiring. This variability could not be completely explained by the location and extent of the lesion, and other factors may play a role. In the CST_{ipsi} group, this large variability may be explained by the amount of overlap of the hotspot within the non-lesioned hemisphere to evoke MEPs in the affected and less-affected hand. Vandermeeren et al. (2009) showed that dexterity indeed varies in individuals with ipsilateral wiring depending on the location of the hotspot of the CST innervating the affected hand and less-affected hand: overlapping hotspots resulted in poorer dexterity, whereas distinct non-overlapping hotspots resulted in a preserved dexterity [40]. Conversely, in the CST_{bilat} group, the large variability may be explained by a predominant contralateral or ipsilateral projection that controls the affected hand, as Jaspers et al. (2016) proposed in their theoretical framework [9]. Altogether, this seems to point toward a distinct underlying pathophysiology of the UL motor impairments in these two CST groups (CST_{ipsi} or CST_{bilat}), suggesting that individuals with either a CST_{bilat} or CST_{ipsi} pattern should be treated as two separate groups for future research. To further unravel the underlying mechanisms of the pathophysiology of motor control and motor capabilities in uCP, additional functional measures should be included such as excitatory and inhibitory intracortical circuits based on TMS (e.g. cortical silent period or paired-pulse paradigms) [15, 41], or functional connectivity of the sensorimotor network based on resting-state functional MRI [42, 43].

We also investigated the impact of the CST wiring and brain lesion characteristics on ***sensory function***, based on the fact that CST projections also extend from the primary sensory cortex and mediate several sensory functions at the level of the spinal cord (control of nociceptive, somatosensory, and somatic motor functions) [44, 45]. Although our simple linear regression analyses suggested that all neurological factors individually played a role in determining sensory function, the multiple prediction model showed that a larger lesion extent, a later lesion (i.e. CSC lesion) and a CST_{ipsi} or CST_{bilat} led to higher chances of developing sensory deficits. Our results are in agreement with a recent study by Gupta et al (2017), who showed that more than 80% of the children with larger extent and later lesions (CSC) had disrupted somatosensory anatomy and physiology (lack of ascending sensory tracts and lack of somatosensory evoked potentials), consequently leading to a loss of sensory function [6]. If the sensory tracts are present, there is evidence suggesting that their main compensatory mechanism is an intra-hemispheric reorganization, i.e. the sensory system reaches the original cortical destination on the post-central gyrus, regardless of lesion timing (PV or CSC lesion) or CST wiring [11, 46, 47]. Current study results suggest that lesion extent best predicts the sensory deficits in individuals with uCP, although lesion timing and CST wiring also play an important role. Future research focussing on the pathophysiology of the sensory system based on non-invasive neurophysiological techniques (e.g. short latency afferent inhibition [48] or sensory evoked potentials [11]), as well as functional connectivity measures, may contribute to increase our understanding of the underlying sensory pathways in uCP.

Lastly, we investigated whether the relationship between motor and sensory function was disrupted by the type of CST wiring. We first confirmed previous study results indicating a significant relation between the motor and sensory outcomes in the total group [1, 25]. However, this association was disrupted by the type of CST wiring, whereby no to little association was shown in the CST_{ipsi} and CST_{contra} groups, but a moderate association was found for the CST_{bilat} group. In the CST_{contra} group, the lack of a significant (or high) correlation seems to be due to the fact that these participants show both adequate motor and sensory function, with little variation in the sensory scale, due to its ordinal nature. This scale used to evaluate sensory function may not be sensitive enough to detect subtle sensory deficits, leading to a possible ceiling effect in the CST_{contra} group. By measuring with more quantitative techniques and devices, e.g. KINARM End-point Lab (BKIN Technologies) [49], we may be able to discern the potential sensory problems that these individuals may present with. Secondly, the sensorimotor dissociation found in the CST_{ipsi} group may be explained at two different levels of the central nervous system. At the level of the spinal cord, the descending CST fibres entering the dorsal horn play an important role in presynaptic inhibition of primary sensory afferent fibres [45, 50], ensuring smooth execution of a movement. A CST_{ipsi} wiring may have consequences in the presynaptic inhibition at the level of the spinal cord and could, consequently, affect the relation between motor and sensory function. On the other hand, at the level of the brain, the intra-hemispheric communication between M1 and S1 has been shown to be very relevant for adequate processing of sensorimotor information [51–53]. As such, the lack of intra-hemispheric cortico-cortical connections may affect the processing of sensory information, having a negative impact on the motor command. On the contrary, the CST_{bilat} group seems to preserve the relation between motor and sensory function, as shown by the stereognosis modality. This may be potentially explained by the predominant behaviour that those with a CST_{bilat} hypothetically show [9]. A relation between adequate sensory and adequate motor function, as seen in the CST_{contra} group may indicate a more ‘contralateral’ behaviour, whilst a disparate relation may be indicative of rather an ‘ipsilateral’ behaviour. However, this needs further confirmation with neurophysiological tools. Although current data do not allow drawing strong conclusions regarding sensorimotor integration, our results highlight the importance of investigating these aspects in the future to better understand the mechanisms of sensorimotor information processing in uCP. By using more advanced techniques to unravel the coupling between the sensory and motor system, we will be able to determine the impact of such dissociation on motor control and motor performance. For instance, short latency afferent inhibition has been put forward as a valuable indicator of the process of bilateral sensorimotor integration [48] and may potentially aid in measuring the reorganization of sensorimotor pathways in uCP.

There might be some important clinical implications based on the results of this study. A better understanding of the underlying mechanisms of motor and sensory impairments will surely contribute to developing new treatment approaches, specifically targeting the individual pathophysiological deficits. First, the type of CST wiring has been investigated as a potential biomarker of treatment response. Although motor improvement does not seem to be CST-type dependent after bimanual training [12, 54], there are conflicting results regarding unimanual training [55–57]. Furthermore, our results highlight the importance of considering the sensory system together with the available motor execution paradigms during UL training. Preliminary results of recent studies have shown the effectiveness of bimanual and sensory training on both motor and sensory function in uCP [58, 59]. To further support interventions targeting sensory deficits, there is evidence in healthy adults suggesting that sensory input can modulate the excitability in both motor cortices simultaneously, as well as the communication between hemispheres [60]. In this line, it seems relevant to combine bimanual and sensory training to enhance the excitability of both motor cortices, which may increase intra- and inter-hemispheric connections between the sensory and motor systems, potentially resulting in long-lasting neuroplastic changes.

Next to the training approaches, it is also important to identify clinically feasible measures to infer the CST wiring and the sensory system. As these assessments are not always pleasant in young children nor practical in a clinical setting, there is a necessity to find tools that are more applicable to daily practice than neurophysiological techniques. To probe the motor system, mirror movements have been put forward as a valid clinical assessment tool that may reflect the underlying individual CST wiring [9, 61]. On the other hand, it seems very challenging to develop an accessible and simple tool to clinically probe the sensory system in uCP. Further research in this field is required to develop quantitative and valid measures of sensory function (e.g. perceptual threshold of touch with electrical stimulation [62] or robotic measures of proprioception [49, 63]) and to link these measures to the underlying mechanisms of the sensory system in uCP.

There are some limitations to be considered for the current study. First, we used scales for the evaluation of lesion location and extent, as well as for assessing sensory function that were based on an ordinal scoring. Although they have been shown to be reliable in uCP [25, 29], such scales may lack sensitivity. Second, our study lacked a neurophysiological technique to probe the sensory system (i.e. sensory evoked potentials), that may contribute to better understand the underlying mechanisms of sensory function in individuals with uCP. Third, the main limitation of the TMS assessment itself lays in the maximum stimulator output intensity that can be reached. This intensity may not have been sufficient to elicit a MEP from either the lesioned or the non-lesioned hemisphere, as the resting motor thresholds are normally higher in children and may be even higher in individuals with uCP. This limitation might have prevented us from finding a CST projection to eventually diagnose the individual as CST_{bilat} or CST_{ipsi} wiring. Furthermore, the MEP data were not analysed, which may provide with useful insights in future studies. Lastly, although our sample size was large and covers the most common lesion timing groups, our results cannot be completely extended to those children with malformations or postnatally acquired brain injuries, as these were not included in the analyses.

Conclusions

CST wiring mainly determines UL motor function, although also lesion extent and damage to the basal ganglia and thalamus significantly contributed to the prediction of UL motor deficits. For sensory function, lesion extent, timing, and the type of CST wiring pattern seem to be important to develop adequate sensory function. The underlying CST wiring seems to disrupt the association between sensory and motor function, pointing toward different mechanisms of sensorimotor integration in uCP. The results of our study contribute to a better understanding of the underlying pathophysiology of motor and sensory function and highlight the importance of investigating sensorimotor integration in future studies. Subsequently, these insights will aid in developing new intervention strategies tailored to the specific deficits of the motor and sensory system of the individual child with uCP.

Data Availability

All data concerning this study is available within the manuscript. Detailed data is available upon request to the first author.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Supplementary materials

Table 1. Descriptive information of the distribution of the lesion location and extent according to the lesion timing groups.

Table 2. Descriptive statistics (X (SD)) and univariate analysis of upper limb motor function according to the CST wiring and the brain lesion characteristics.

Table 3. Descriptive statistics (Me (IQR)) and univariate analysis of upper limb sensory function (3A, stereognosis and 3B, two-point discrimination and thresholds of touch sensation) according to the CST wiring and the brain lesion characteristics.

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