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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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#### 14 Abstract

15 Brain lesion characteristics (timing, location, and extent) and the type corticospinal tract

16 (CST) wiring have been proposed as determinants of upper limb (UL) motor function in

17 unilateral cerebral palsy (uCP), yet an investigation of the relative combined impact of these

18 factors on both motor and sensory function is still lacking. Here, we first investigated

19 whether structural brain lesion characteristics could predict the underlying CST wiring, and

20 we explored the role of CST wiring and brain lesion characteristics to predict UL motor and

21 sensory function in uCP.

22 Fifty-two participants with uCP (mean age (SD): 11y3m (3y10m)) underwent a single-pulse

23 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

25 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

27 with a semi-quantitative scale. A standardized protocol included UL motor (grip strength,

28 unimanual capacity, bimanual performance) and sensory measures.

29 A combination of lesion locations (damage to the PLIC and frontal lobe) significantly 30 contributed to differentiate between the CST wiring groups, re-classifying the participants in 31 their original group with 57% of accuracy. Motor and sensory function were influenced by 32 each of the investigated neurological factors. However, in a multiple regression analysis, 33 motor function was predicted by the type of CST wiring (more preserved in individuals with 34 contralateral CST wiring (p<0.01)), lesion extent and damage to the basal ganglia and 35 thalamus. Sensory function seemed to be best predicted by the combination of a large and 36 later lesion, and an ipsilateral or bilateral CST wiring, which led to increased sensory deficits 37 (p<0.05).

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

# 40 Introduction

41 Upper limb (UL) function is commonly impaired in individuals with unilateral cerebral palsy 42 (uCP), negatively impacting on daily life activities [1]. The large variability in the clinical 43 presentation of UL function, but also in treatment response, has resulted in increasing interest 44 in understanding the underlying neural mechanisms that determine UL function, and its 45 contribution to further optimize therapy planning for the individual with uCP. A number of 46 neurological factors have been put forward as potential predictors of UL function, i.e. the 47 structural brain lesion characteristics (i.e. lesion timing, location, and extent) and the type of 48 corticospinal tract (CST) wiring [2–6].

49 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<sup>st</sup> and 2<sup>nd</sup> trimester of pregnancy), 50 periventricular lesion (PV, early 3<sup>rd</sup> trimester), cortico-subcortical lesions (CSC, late 3<sup>rd</sup> 51 52 trimester and around birth) [7]. Previous studies investigating the impact of lesion timing on 53 UL function have shown that individuals with a later lesion (i.e. CSC lesions) present with 54 poorer UL motor and sensory function [2, 3, 5]. Besides lesion timing, lesion location and 55 extent have shown to play an important role in determining UL function, whereby damage to 56 the posterior limb of the internal capsule (PLIC) and the basal ganglia, and a larger lesion 57 extent are related to worse UL motor and sensory function [2, 3] However, there is still large 58 variability in UL function that remains unexplained based on these factors.

59 The unilateral brain damage in individuals with uCP can also result in a partial or complete 60 reorganization of the CST towards the non-lesioned hemisphere [8]. This reorganization of 61 the CST wiring is unique in uCP and refers to the efferent motor input to the affected hand. 62 Researchers have identified three types of CST wiring, i.e. contralateral (CST<sub>contra</sub>, the 63 affected hand receives input from the crossed CST, originating in the lesioned hemisphere), 64 ipsilateral (CST<sub>ipsi</sub>, the affected hand receives input from the uncrossed CST, originating in 65 the non-lesioned hemisphere) and bilateral (CST<sub>bilat</sub>, the affected hand receives input from 66 both the crossed and uncrossed CST, originating in the lesioned and non-lesioned 67 hemisphere, respectively) [8, 9]. It has been suggested that the type of CST wiring is the main 68 factor influencing UL function, whereby individuals with CST<sub>contra</sub> present with more 69 preserved UL function compared to the other groups [6, 10–13]. Nevertheless, assessing the 70 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.

74 Whilst the role of lesion timing, location and extent has been well investigated [2, 3, 14], 75 only a few studies examined the impact of the CST wiring on UL function, and they often 76 have several limitations (i.e. small sample sizes, ordinal scoring of impairments, limited to 77 motor deficits) [5, 10, 15]. Moreover, studies thus far focused on each factor independently, 78 whereas only one study described the impact of the CST wiring and lesion timing on UL 79 function in uCP [10], and only one study reports the impact of CST wiring and lesion extent 80 in children with PV lesions [4]. Although the authors suggested the relevance of both lesion 81 timing and type of CST wiring in predicting UL function, the small sample size, the lack of a 82 standardized evaluation of motor function, and the merely descriptive nature of the study, 83 hampered the possibility of drawing strong conclusions. Furthermore, it has been shown that 84 an intact sensory function is essential to develop an adequate motor function in other 85 neurological disorders (such as adult stroke) [16, 17]. Also in individuals with uCP, sensory 86 and motor function are highly related [1], although the impact of the CST wiring on this 87 relationship remains unknown.

88 In this study, we investigated the impact of CST wiring and structural brain lesion 89 characteristics on UL motor and sensory function in a large group of individuals with uCP, 90 using a systematic and comprehensive evaluation. Our first hypothesis is that the type of CST 91 wiring pattern in unilateral CP can be predicted based on a linear combination of measures of 92 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 93 94 sensory function than any of these factors alone. Last, we speculate that the relation between 95 motor and sensory function is disrupted by the type of CST wiring.

96

# 97 Materials and Methods

#### 98 Participants

Children and adolescents with uCP aged between 5-21 years old were recruited via the CP 99 100 reference center of the University Hospitals Leuven between 2014 and 2017. They were 101 excluded if they (1) received UL botulinum toxin injections six months prior to the 102 assessment, (2) had UL surgery two years prior to the assessment and/or (3) had other 103 neurological or genetic disorders. All individuals assented to participate, all parents signed 104 the informed consent (participants younger than 18 years old), and participants older than 12 105 years also signed the informed consent, in accordance with the declaration of Helsinki. This 106 study was approved by the Medical Ethical Committee of the University Hospital Leuven 107 (S55555 and S56513).

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

#### 114 Upper limb evaluation

#### 115 Motor function

- 116 Grip strength, unimanual capacity and bimanual performance composed the motor
- 117 evaluation. Maximum *grip strength* was assessed using the Jamar® hydraulic hand
- 118 dynamometer (Sammons Preston, Rolyan, Bolingbrook, IL, USA). The less-affected hand
- 119 was measured first and the mean of three maximum contractions was calculated per hand.
- 120 The ratio between hands was used for further analyses to cancel out the effect of age (grip
- 121 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-
- 123 affected hand). Unimanual capacity was assessed with the Jebsen-Taylor hand function test
- 124 (JTHFT). The JTHFT reliably measures movement speed during six unimanual tasks [18,
- 125 19]. Similar to other studies, we used a modified version for children and adolescents with
- 126 uCP in which the writing task was removed, and the time to carry out each task was reduced

127 from 3 to 2 minutes to avoid frustration [19, 20]. The time to perform every task was summed 128 up and the ratio between hands was used for further analyses to cancel out the effect of age 129 (JTHFT ratio = JTHFT affected hand/JTHFT less-affected hand, whereby a lower score 130 (closer to 1) indicates movement speed in the affected hand similar to that of the less-affected 131 hand). Bimanual performance was evaluated with the Assisting Hand Assessment (AHA), 132 which assesses how effectively the affected hand is used in bimanual activities [21-23]. The 133 spontaneous use is evaluated during a semi-structured play session with standardized toys 134 requiring bimanual handling. Given the age range of the participants of this study, the School 135 Kids AHA and the Ad-AHA were administered [22, 24]. The AHA was scored by certified 136 raters (LM and CSM), using the 5.0 version which includes 20 items that are scored from 0 137 ('does not do') to 4 ('effective use'), resulting in a final score between 0-100 AHA units.

#### 138 Sensory function

139 Sensory assessments comprised measures of exteroception (tactile sense), proprioception

- 140 (movement sense), two-point discrimination (2PD, Aesthesiometer®) and stereognosis
- 141 (tactile object identification), which have been shown to be reliable in this population [25].
- 142 Tactile and movement sense were classified as normal (score 2), impaired (score 1) or absent
- 143 (score 0). 2PD was classified according to the width between the two points that the
- 144 participants could discriminate: normal (0-4mm, score 2), or impaired (>4mm, score 1) [26].
- 145 Tactile object identification was used as the number of objects that the children could
- 146 recognize (0-6). In addition, a kit of 20 nylon monofilaments (0.04g 300g) (Jamar®
- 147 Monofilaments, Sammons Preston, Rolyan, Bolingbrook, IL, USA) was used to reliably
- 148 determine threshold values for touch sensation [27, 28]. Touch sensation was categorized as
- 149 normal (0.008-0.07g), diminished light touch (0.16-0.4g), diminished protective sensation
- 150 (0.6-2g), loss of protective sensation (4.19-180g) and untestable (300g), according to the
- 151 manual (Jamar® Monofilaments, Sammons Preston, Rolyan, Bolingbrook, IL, USA).

#### 152 Structural MRI

- 153 Structural images were acquired using three-dimensional fluid-attenuated inversion recovery
- 154 (3D FLAIR) [321 slices, slice thickness = 1.2 mm, slice gap = 0.6 mm, repetition time = 4800
- 155 ms, echo time = 353 ms, field of view (FOV) =  $250 \times 250$  mm<sup>2</sup>,  $1.1 \times 1.1 \times 0.56$  mm<sup>3</sup> voxel
- size, acquisition time = 5 minutes]. In addition, magnetization prepared rapid gradient echo
- 157 (MPRAGE) was acquired [182 slices, slice thickness = 1.2 mm, slice gap = 0 mm, TR =

9.7ms, TE = 4.6ms, FOV = 250x250mm<sup>2</sup>, 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).

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

167 Lesion location and extent was determined using a semi-quantitative scale recently 168 developed by Fiori et al (2014) [29]. The scale consists of a graphical template with six axial 169 slices of the brain, and an extra template for the basal ganglia (lenticular and caudate), 170 thalamus, posterior limb of the internal capsule (PLIC), brainstem, corpus callosum, and 171 cerebellum. Firstly, the slices corresponding to the template slices are to be found and the 172 lesion is drawn onto the template. Next, the damage to the periventricular, middle and 173 cortico-subcortical layers of each lobe are scored for both hemispheres separately. The sum 174 of the damage to each lobe results in the lobar score, ranging from 0-3 for each lobe. Damage 175 to the basal ganglia (lenticular and caudate), thalamus, PLIC, and brainstem directly is 176 binarily scored from the MRI (affected or non-affected). Damage to the corpus callosum is 177 scored from 0-3, based on the involvement of the anterior, middle and posterior thirds of the 178 corpus callosum on a sagittal view. Last, the involvement of the cerebellum is based on 179 damage to the vermis (0-1) and each of the hemispheres (0-2), resulting in a total score 180 ranging from 0-3. A total ipsilesional score is calculated based on the damage to the lobes (0-181 3 for each lobe, i.e. total of 0-12) and damage to the subcortical structures (0-5; ranging from 182 0-17). More detailed information about the scale and its scoring procedure can be found in 183 the respective study [29]. This semi-quantitative scale has been shown valid and reliable in 184 children with uCP [29, 30].

185 In the present study, lesion **location** was indicated by the damage to the frontal and parietal

186 lobes (0-4), damage to the basal ganglia and thalamus (0-3), and damage to the PLIC (0-1).

187 These locations were chosen based on their relation to the sensorimotor system [31]. Lesion

188 **extent** was indicated by the total ipsilesional score (0-17).

#### **Transcranial Magnetic Stimulation**

190 Single-pulse TMS was conducted to assess CST wiring. TMS was applied using a MagStim 191 200 Stimulator (Magstim Ltd, Whitland, Wales, UK) equipped with a focal 70mm figure-192 eight coil and a Bagnoli electromyography (EMG) system with two single differential surface 193 electrodes (Delsys Inc, Natick, MA, USA). A Micro1401-3 acquisition unit and Spike 194 software version 4.11 (Cambridge Electronic Design Limited, Cambridge, UK) were used to 195 synchronize the TMS stimuli and the EMG data acquisition. Motor Evoked Potentials 196 (MEPs) were bilaterally recorded from the muscles opponens pollicis brevis. During the TMS 197 assessment, participants wore a cap that allows creating a grip with a coordinate system to 198 identify the optimal point to stimulate (hotspot) in a standardized and systematic way. The 199 hotspot and the resting motor threshold (RMT, defined as the minimum intensity required to 200 obtain 5/10 MEP of at least  $50\mu$ V in the corresponding muscle) were identified by starting 201 the stimulation intensity at 30% with an incremental increase of 5% [4]. For each 202 hemisphere, stimulation started from the assumed "motor hotspot", which is located 5cm 203 lateral and 1cm anterior from the scalp middle point (Cz), at 30%. After approximately 2-3 204 pulses, the stimulation intensity was increased 5% for another 2-3 pulses, until MEPs were 205 found. If no MEP can be elicited after increasing up to 60 to 80%, the coil would be moved to 206 a different location on the scalp grid, and the procedure would be repeated until an MEP was 207 elicited. Stimulation up to 100% of the maximum stimulator output was continued until an 208 MEP was elicited. The non-lesioned hemisphere was always stimulated first and allowed to 209 identify contralateral CST projections to the less-affected hand. Stimulation in the non-210 lesioned hemisphere was continued up to 100% of the maximum stimulator output to search 211 for possible ipsilateral CST projections to the affected hand. Next, the lesioned hemisphere 212 was stimulated to identify possible contralateral CST projections to the affected hand. If only 213 contralateral MEPs from each hemisphere were found, the child was categorized as having a 214 CST<sub>contra</sub> wiring. If MEPs in the affected hand were evoked from both hemispheres, the child 215 was categorized as having a CST<sub>bilat</sub> wiring. Lastly, if MEPs in the impaired hand were only 216 evoked when stimulating the non-affected hemisphere, the child was categorized as having a 217 CST<sub>ipsi</sub> wiring. TMS measures have been shown to be reliable in adults [32, 33] and in 218 children [34]. In this study, the TMS assessment was used for diagnostic purposes. In cases 219 when high intensities were not tolerated, the stimulation intensity was increased up to at least 220 80% of the maximum stimulator output and children were asked to hold a pen to ensure pre-221 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 wiringpattern.

#### 224 Statistical analyses

225 First, descriptive statistics were used to document the distribution of brain lesion 226 characteristics according to the CST wiring. Next, we investigated the differences in 227 occurrence of lesion timing, location, and extent between the CST wiring groups by using 228 analysis of contingency tables (Chi-Square and Fisher's exact test), Kruskal-Wallis test 229 (ordinal data), and ANOVA (lesion extent). Lastly, we used discriminant analysis to explore 230 whether the type of CST wiring would differ depending on the linear combination of lesion 231 timing, location, and extent, in a multivariate way. Cross-validation procedure was included 232 to investigate the accuracy of the model in reclassifying the participants in the original CST 233 wiring groups. Variables related to lesion timing, lesion location (damage to the frontal lobe, 234 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.

236 To investigate the impact of the type of CST wiring and brain lesion characteristics on UL 237 function, we first used linear simple regression and then multiple regression analysis to 238 investigate the combined impact of these factors on UL motor and sensory function. For the 239 continuous variables related to motor function, normality was first verified by inspecting the 240 histograms and with the Shapiro-Wilk test, showing a normal distribution only for the AHA. 241 For the JTHFT ratio and the grip strength ratio, a logarithmic transformation was applied (y' 242  $= \log 10$  (y)). To investigate the impact of the type of CST wiring and brain lesion 243 characteristics on UL motor function, we computed a multiple regression analysis. Similarly, 244 for UL sensory function, we conducted a simple ordinal logistic regression for stereognosis 245 and thresholds for touch sensation, and a simple logistic regression for 2PD to investigate the 246 impact of each individual neurological factor on the sensory function. Next, we performed 247 multiple regression analyses (ordinal and logistic) to investigate the combined impact of the 248 neurological predictors on the sensory deficits. The predictors included in the multiple 249 regression model were the type of CST wiring, lesion timing, location (damage to the frontal 250 lobe, parietal lobe, PLIC, and basal ganglia and thalamus), and ipsilesional extent of the 251 lesion. To predict both motor and sensory function, interaction terms were built between the 252 CST wiring and (i) lesion timing, and (ii) lesion extent, and included in the model. The

- 253 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),
- 259 high (0.70-0.90) and very high correlation (>0.90) [35].
- 260 In addition, effects sizes were calculated for the comparisons and interpreted according to
- 261 Cohen, depending on the computed test:  $\eta^2$  (partial etha squared) for the prediction models
- 262 (small 0.01, medium 0.06, large 0.14) [36, 37]. Statistical significance was set at  $\alpha$ <0.05 for
- 263 main tests with Bonferroni correction for post-hoc tests. All statistical analyses were
- 264 computed with SPSS Statistics for Windows version 24.0 (IBM Corp. Armonk, NY: IBM
- 265 Corp.).

# 266 **Results**

# 267 Participants

268 Seventy-five children and adolescents with uCP participated in this study (mean age (SD): 269 11y1m (3y6m); 33 girls; 39 left uCP). According to the Manual Ability Classification System 270 (MACS), 25 individuals were classifed as MACS I, 25 as MACS II and 25 as MACS III. 271 Sixteen participants did not have CST wiring data (n=1 panic attack, n=2 hemispherectomy, 272 n=3 VP shunt, n=2 epilepsy, n=1 tumor, n=4 refusals to participate, n=3 inconclusive TMS 273 results), resulting in a total of 59 participants. The TMS assessment identified 20 individuals 274 with CST<sub>contra</sub>, 18 with CST<sub>bilat</sub> and 21 with CST<sub>ipsi</sub>. For the analyses in this study, 275 participants with malformations (n=1), acquired lesions (n=4) or no visible lesions (n=2) 276 were excluded due to the very small sample size of these sub-groups, resulting in a total 277 group of 52 participants (mean age (SD): 11y4m (3y10m); 22 girls; 28 left uCP) with 278 available CST wiring (n=17 contralateral; n=19 ipsilateral; n=16 bilateral) and data related to 279 the timing, location, and extent of the lesion. A summary of the lesion locations and extent 280 according to the lesion timing is provided in Supplementary materials (Table 1). Thirty-four 281 individuals had a PV lesion and 18 had a CSC lesion. Clinical motor and sensory data was 282 missing in one participant (boy, 19y7m, PV lesion, and CST<sub>contra</sub> wiring) and sensory data

was evaluated in a subsample of participants (see sensory function results section for moredetails).

#### 285 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
- 291 wiring (Wilks'  $\lambda = 0.611$ , Chi-square = 23.88, df = 4, Canonical correlation = 0.602, p <
- 292 0.001). The two functions extracted accounted for nearly 57% of the variance in the type of
- 293 CST wiring. The standardized discriminant function coefficients of the two extracted
- 294 functions indicated the contribution of each retained independent variable (damage to the
- 295 PLIC and damage to the frontal lobe) to each function, showing how strongly the
- 296 discriminant variables affect the score. These coefficients can be then used for the
- 297 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
- 299 lobe).
- 300

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

			CST wiring			
			Contralateral	Bilateral	Ipsilateral	p-value
Timing						
Lesion timing $^{\text{F}}$	PV	N (%)	15 (88.2%)	8 (50%)	11 (57.9%)	0.04
	CSC		2 (11.8)	8 (50%)	8 (42.1%)	
Location						
PLIC <sup>¥</sup>	Not affected	N (%)	8 (47%)	1 (6%)	0 (0%)	< 0.001
	Affected		9 (53%)	15 (94%)	19 (100%)	
Basal ganglia and	l thalamus <sup>◊</sup>	Me (p25-p75)	0 (0-1)	1.50 (0 (2.50)	1 (1-2)	0.006 <sup>a,b</sup>
Frontal Lobe $^{\diamond}$		Me (p25-p75)	1 (1-1)	1.50 (1-2.25)	1 (1-1.50)	0.004 <sup>a,b</sup>
Parietal Lobe $^{\Diamond}$		Me (p25-p75)	2 (1-2)	2 (1.25-3)	2 (2-2.50)	0.09
Extent						
Ipsilesional exten	t°	X (SD)	5.18 (3.07)	8.38 (3.95)	9.05 (3.27)	0.004 <sup>a,b</sup>

310 CST, corticospinal tract; PV, periventricular; CSC, cortico-subcortical; PLIC, posterior limb

311 of the internal capsule. <sup>¥</sup>Chi-Square statistic, <sup>§</sup>Fisher's exact test, <sup>◊</sup>Kruskal-Wallis test,

312 °ANOVA. <sup>a</sup> Contralateral vs. Ipsilateral; <sup>b</sup> Contralateral vs. Bilateral.

313

314 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<sub>ipsi</sub> group, 47.1% in the

316 CST<sub>contra</sub> group, and only 31.3% in the CST<sub>bilat</sub> 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<sub>contra</sub> (-1.05, 0.01); CST<sub>ipsi</sub> (0.48, -0.23); CST<sub>bilat</sub> (0.54, 0.26)].

321

#### 322 CST wiring, brain lesion characteristics and UL function

#### 323 Motor function

324 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

326 linear regression analyses to predict motor function based on a single neurological factor

- 327 showed that every factor had an influence on motor function (grip strength, p<0.04; JTHFT,
- 328 p<0.004; AHA, p<0.01; see Supplementary materials Table 2 for detailed information).

329 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

331 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
- 333 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
- 336 (F(2, 51)=12.20; p<0.0001;  $\eta^2$ =0.34, R<sup>2</sup>=46%) and the total extent of the lesion (F(1,

- 337 51)=8.05; p=0.007;  $\eta^2$ =0.15,  $\Delta R^2$ =8%). For **bimanual performance** (AHA), the regression
- 338 model explained 61% of the variance, with the type of CST wiring (F(2, 51)=19.03;
- 339 p<0.0001;  $\eta^2$ =0.45,  $\Delta R^2$ =52%), the total extent of the lesion (F(1, 51)=10.65; p<0.001;
- 340  $\eta^2=0.19$ ,  $\Delta R^2=5\%$ ), and the damage to the basal ganglia and thalamus (F(1, 51)=4.90;
- 341 p=0.03;  $\eta^2$ =0.10,  $\Delta R^2$ =4%) significantly contributing to the model (Fig 2). No interaction
- 342 effects were identified for any of the motor outcome variables.
- 343 Table 2. Descriptive statistics of the observed and estimated marginal means of upper limb
- 344 motor function according to the CST wiring groups.

	Estimated marginal means and SD			
	CST <sub>contra</sub> CST <sub>ipsi</sub> CST <sub>bilat</sub>			
	( <b>n=16</b> )	( <b>n=19</b> )	( <b>n=16</b> )	
Grip strength ratio (log)	0.14 (0.13) <sup>a</sup>	0.55 (0.20) <sup>a</sup>	0.46 (0.24) <sup>a</sup>	
JTHFT ratio (log)	0.30 (0.24) <sup>b</sup>	0.67 (0.23) <sup>b</sup>	0.64 (0.22) <sup>b</sup>	
AHA (0-100)	79.66 (10.28) <sup>c</sup>	58.70 (9.81) <sup>c</sup>	61.58 (9.67) <sup>c</sup>	

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

350





352 Fig 2. Upper limb motor function differs in individuals with CST<sub>contra</sub> compared to those with

- 353 CST<sub>bilat</sub> or CST<sub>ipsi</sub> 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.
- 357 AHA, Assisting Hand Assessment; JTHFT, Jebsen Taylor Hand Function Test; CST,
- 358 corticospinal tract. p<0.01; p<0.001. Estimated Marginal Means are adjusted according to 350 the significant covariates (see Table 2 for details)
- 359 the significant covariates (see Table 2 for details).

#### 360 Sensory function

361 Descriptive information of sensory function according to each neurological factor is

362 summarized in Table 3 of Supplementary materials. Sensory function data (tactile sense,

363 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

- 365 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.
- 367 The simple linear analyses to predict sensory function based on a single neurological
- 368 predictor indicated that every predictor impacted on stereognosis (p<0.032). In contrast, 2PD
- 369 was influenced by all neurological predictors (p<0.04) except the damage to the PLIC
- 370 (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).

- 372 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
- 374 contributing to the model. For **stereognosis**, the retained main effects were the CST wiring
- 375 (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
- 377 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
- 379  $CST_{contra}$  wiring show 10.23 and 9.7 times higher probability of having better scores in the
- 380 stereognosis test compared to those with a CST<sub>ipsi</sub> or CST<sub>bilat</sub>, respectively (p=0.02), whilst
- there was no difference between the last two (p=0.34). Lastly, the odds of having higher
- 382 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
- 384 characteristics to predict deficits in stereognosis (p>0.05)
- 385 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
- 387 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
- 389 odds of having impaired 2PD increase by 1.34 for every unit change in the ipsilesional extent

- 390 of the lesion (p=0.05). No interactions were found between the CST wiring and the brain
- 391 lesion characteristics to predict deficits in 2PD (p>0.05)
- 392 Table 3. Descriptive statistics of the sensory function (3A, stereognosis (number of correctly
- 393 recognized objects; 3B, two-point discrimination; 3C, touch sensation) according to each of
- 394 the variables significantly contributing to each prediction model.

Ta	ble	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								
Contralatera l	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	Impaired	
		(≤4mm)	(>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 (-)

395 PV, periventricular lesion; CSC, cortico-subcortical lesion; CST, corticospinal tract; N,

396 number of cases; Me, median; IQR, interquartile range.

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

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

- 405 The correlation analyses between the motor and sensory function for the whole group
- 406 indicated a moderate association between the stereognosis score and grip strength ratio ( $r_s = -$

407 0.60, p<0.001), JTHFT ratio ( $r_s = -0.60$ , p<0.001) and AHA ( $r_s = 0.61$ , p<0.001).

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

413 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<sub>contra</sub> and CST<sub>ipsi</sub> showed no to low correlations, whereas those
with CST<sub>bilat</sub> showed moderate correlations. Each dot represents an individual child, with
CST<sub>contra</sub> (blue), CST<sub>bilat</sub> (green), and CST<sub>ipsi</sub> (orange). Correlations between stereognosis

- 419 with grip strength ratio (ratio, i.e. closer to one indicates preserved grip strength), JTHFT
- 420 ratio (ratio, i.e. closer to one indicates preserved grip strength), and AHA. Correlation
- 421 coefficients correspond to the analysis for the whole group.
- 422

# 423 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.

429 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 430 431 timing, location and extent were significantly different between the CST wiring groups. Our 432 results showed that a CST<sub>contra</sub> was only seen in 2 out of 18 children with a CSC lesion, 433 compared to 15 out of 34 children with a PV lesion. Current results suggest that damage to 434 cortical and/or subcortical structures (i.e. CSC lesion), reduces the potential of the CST to 435 develop according to its typical contralateral trajectory. We hypothesise that this is likely 436 driven by the reduced neural activity in the motor cortical areas after a CSC lesion, which are 437 crucial for the development of the CST during the postnatal period [38]. However, a 438 contralateral development of the CST is still possible in CSC lesions, and it may occur 439 differently depending on lesion location and extent.

Once all predictors were simultaneously entered in a multiple linear analysis, we found that 440 441 the combination of the damage to the PLIC and the frontal lobe significantly discriminated 442 between the CST wiring groups. Half of the children in the CST<sub>contra</sub> group showed damage 443 to the PLIC, in contrast to the 94% and 100% in the CST<sub>bilat</sub> and CST<sub>ipsi</sub> group who showed 444 damage to this white matter bundle. Furthermore, the frontal lobe was also more damaged in the CST<sub>bilat</sub> and CST<sub>ipsi</sub> groups, compared to the CST<sub>contra</sub>. Although it is not unexpected that 445 446 the PLIC and the frontal lobe are the two significant predictors in the model, due to their 447 undoubtable relation with the motor cortex and the performance of actions, this is the first 448 time that this interaction with the type of CST wiring is shown. Contrary to the importance of 449 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.

454 Next to the predictive model, we also investigated how accurate the two functions derived 455 from the discriminant analysis would be to reclassify the individuals in their original 456 categories. Despite the significant contribution of the PLIC and the frontal lobe to the 457 discriminant model, the classification accuracy only reached 57%, suggesting that timing, 458 location and extent of the lesion (as included in the model) do not provide sufficient accurate 459 information to predict the underlying type of CST wiring. Notwithstanding the validity and 460 reliability of the semi-quantitative scale that was used to investigate lesion location and 461 extent, we acknowledge that the semi-quantitative character of the scale may have 462 underestimated the predictive value of the structural brain damage. Therefore, these results 463 should be replicated in the future with volumetric measures of the different brain structures. 464 For example, the projections to the PLIC have been shown to be topographically organized 465 with reduced microstructural integrity in children with uCP [39] by using diffusion measures. 466 Investigating the volumetric damage to the frontal lobe and the microstructural integrity of 467 the PLIC may provide with further insights in determining the type of CST wiring in uCP.

468 For our second research question, we investigated the impact of CST wiring and brain lesion 469 characteristics (timing, location, and extent) on motor and sensory function. Regarding motor 470 outcome, simple linear regression analyses indicated that the CST wiring and all brain lesion 471 characteristics had an influence on the grip strength, manual dexterity and bimanual 472 performance, which confirmed what previous studies have shown [5, 6, 10]. However, in the 473 multiple linear regression analysis, we found that the underlying CST wiring plays a major, 474 but not unique, role in determining UL motor function, as lesion location and extent also 475 significantly contributed to increasing the explained variance for the JTHFT and for the 476 AHA. Specifically, the type of CST wiring explained 46% and 52% of the JTHFT and the 477 AHA variances, respectively, which was increased up to 54% and 61% by including lesion 478 extent and damage to the basal ganglia and thalamus into the model. In general, our results 479 show that a CST<sub>ipsi</sub> or CST<sub>bilat</sub> lead to poorer UL motor function compared to CST<sub>contra</sub> for all 480 motor outcomes, even when controlling for the significant contribution of lesion extent and 481 location. The importance of the underlying CST wiring is an expected result, as the CST is

482 the main motor drive and its damage causes vast disturbances on voluntary motor control, 483 drastically reducing motor capabilities [38]. Whilst lesion timing, location, and extent have 484 been put forward as a predictor of UL function [2, 3] and was also confirmed in our linear 485 regression analysis, the huge variability in motor function reported by previous studies seems 486 to be mainly explained by the underlying CST wiring. Staudt et al. (2004) were the first to 487 report on the relation between CST reorganization potential at different gestational ages and 488 UL motor function [10]. These authors also found that, along with the CST wiring, UL motor 489 function further worsened in later lesions (CSC lesions) [10]. Linear regression analysis also 490 showed that later lesions led to poor motor outcome, but multiple regression analysis 491 revealed that lesion location and extent were key factors, next to the type of CST wiring. 492 Although later lesions seem to be associated to a larger extent [3], it seems that the lesion 493 extent itself plays a more important role in motor outcome, i.e. children with a PV lesion with 494 large extent will also present with poorer hand function. Interestingly, the damage to the 495 basal ganglia and thalamus explained an extra 4% of the variability in the AHA. In 496 accordance with our results, previous studies have reported the negative impact of these 497 subcortical structures on UL motor outcome [2, 5].

498 It is important to note that we still found large variability in the three motor outcome 499 measures within both the CST<sub>ipsi</sub> and CST<sub>bilat</sub> groups, whereas the variability in the CST<sub>contra</sub> 500 group was rather small (Fig 2, see also Table 2 Supplementary materials for observed means). In other words, some individuals with a CST<sub>ipsi</sub> and CST<sub>bilat</sub> had good motor 501 502 function, similar to those with a CST<sub>contra</sub> wiring. This variability could not be completely 503 explained by the location and extent of the lesion, and other factors may play a role. In the 504 CST<sub>ipsi</sub> group, this large variability may be explained by the amount of overlap of the hotspot 505 within the non-lesioned hemisphere to evoke MEPs in the affected and less-affected hand. 506 Vandermeeren et al. (2009) showed that dexterity indeed varies in individuals with ipsilateral 507 wiring depending on the location of the hotspot of the CST innervating the affected hand and 508 less-affected hand: overlapping hotspots resulted in poorer dexterity, whereas distinct nonoverlapping hotspots resulted in a preserved dexterity [40]. Conversely, in the CST<sub>bilat</sub> group, 509 510 the large variability may be explained by a predominant contralateral or ipsilateral projection 511 that controls the affected hand, as Jaspers et al. (2016) proposed in their theoretical 512 framework [9]. Altogether, this seems to point toward a distinct underlying pathophysiology 513 of the UL motor impairments in these two CST groups (CST<sub>ipsi</sub> or CST<sub>bilat</sub>), suggesting that 514 individuals with either a CST<sub>bilat</sub> or CST<sub>ipsi</sub> pattern should be treated as two separate groups

- 515 for future research. To further unravel the underlying mechanisms of the pathophysiology of
- 516 motor control and motor capabilities in uCP, additional functional measures should be
- 517 included such as excitatory and inhibitory intracortical circuits based on TMS (e.g. cortical
- 518 silent period or paired-pulse paradigms) [15, 41], or functional connectivity of the
- sensorimotor network based on resting-state functional MRI [42, 43].

520 We also investigated the impact of the CST wiring and brain lesion characteristics on sensory 521 *function*, based on the fact that CST projections also extend from the primary sensory cortex 522 and mediate several sensory functions at the level of the spinal cord (control of nociceptive, 523 somatosensory, and somatic motor functions) [44, 45]. Although our simple linear regression 524 analyses suggested that all neurological factors individually played a role in determining 525 sensory function, the multiple prediction model showed that a larger lesion extent, a later 526 lesion (i.e. CSC lesion) and a CST<sub>ipsi</sub> or CST<sub>bilat</sub> led to higher chances of developing sensory 527 deficits. Our results are in agreement with a recent study by Gupta et al (2017), who showed 528 that more than 80% of the children with larger extent and later lesions (CSC) had disrupted 529 somatosensory anatomy and physiology (lack of ascending sensory tracts and lack of 530 somatosensory evoked potentials), consequently leading to a loss of sensory function [6]. If 531 the sensory tracts are present, there is evidence suggesting that their main compensatory 532 mechanism is an intra-hemispheric reorganization, i.e. the sensory system reaches the 533 original cortical destination on the post-central gyrus, regardless of lesion timing (PV or CSC 534 lesion) or CST wiring [11, 46, 47]. Current study results suggest that lesion extent best 535 predicts the sensory deficits in individuals with uCP, although lesion timing and CST wiring 536 also play an important role. Future research focussing on the pathophysiology of the sensory 537 system based on non-invasive neurophysiological techniques (e.g. short latency afferent 538 inhibition [48] or sensory evoked potentials [11]), as well as functional connectivity 539 measures, may contribute to increase our understanding of the underlying sensory pathways 540 in uCP.

- 541 Lastly, we investigated whether the relationship between motor and sensory function was
- 542 disrupted by the type of CST wiring. We first confirmed previous study results indicating a
- 543 significant relation between the motor and sensory outcomes in the total group [1, 25].
- 544 However, this association was disrupted by the type of CST wiring, whereby no to little
- 545 association was shown in the CST<sub>ipsi</sub> and CST<sub>contra</sub> groups, but a moderate association was
- 546 found for the CST<sub>bilat</sub> group. In the CST<sub>contra</sub> group, the lack of a significant (or high)

547 correlation seems to be due to the fact that these participants show both adequate motor and 548 sensory function, with little variation in the sensory scale, due to its ordinal nature. This scale 549 used to evaluate sensory function may not be sensitive enough to detect subtle sensory 550 deficits, leading to a possible ceiling effect in the CST<sub>contra</sub> group. By measuring with more 551 quantitative techniques and devices, e.g. KINARM End-point Lab (BKIN Technologies) 552 [49], we may be able to discern the potential sensory problems that these individuals may 553 present with. Secondly, the sensorimotor dissociation found in the CST<sub>ipsi</sub> group may be 554 explained at two different levels of the central nervous system. At the level of the spinal cord, 555 the descending CST fibres entering the dorsal horn play an important role in presynaptic 556 inhibition of primary sensory afferent fibres [45, 50], ensuring smooth execution of a 557 movement. A CST<sub>ipsi</sub> wiring may have consequences in the presynaptic inhibition at the level 558 of the spinal cord and could, consequently, affect the relation between motor and sensory 559 function. On the other hand, at the level of the brain, the intra-hemispheric communication 560 between M1 and S1 has been shown to be very relevant for adequate processing of 561 sensorimotor information [51–53]. As such, the lack of intra-hemispheric cortico-cortical 562 connections may affect the processing of sensory information, having a negative impact on 563 the motor command. On the contrary, the CST<sub>bilat</sub> group seems to preserve the relation 564 between motor and sensory function, as shown by the stereognosis modality. This may be 565 potentially explained by the predominant behaviour that those with a CST<sub>bilat</sub> hypothetically 566 show [9]. A relation between adequate sensory and adequate motor function, as seen in the 567 CST<sub>contra</sub> group may indicate a more 'contralateral' behaviour, whilst a disparate relation may 568 be indicative of rather an 'ipsilateral' behaviour. However, this needs further confirmation 569 with neurophysiological tools. Although current data do not allow drawing strong 570 conclusions regarding sensorimotor integration, our results highlight the importance of 571 investigating these aspects in the future to better understand the mechanisms of sensorimotor 572 information processing in uCP. By using more advanced techniques to unravel the coupling 573 between the sensory and motor system, we will be able to determine the impact of such 574 dissociation on motor control and motor performance. For instance, short latency afferent 575 inhibition has been put forward as a valuable indicator of the process of bilateral 576 sensorimotor integration [48] and may potentially aid in measuring the reorganization of 577 sensorimotor pathways in uCP.

578 There might be some important clinical implications based on the results of this study. A 579 better understanding of the underlying mechanisms of motor and sensory impairments will

580 surely contribute to developing new treatment approaches, specifically targeting the 581 individual pathophysiological deficits. First, the type of CST wiring has been investigated as 582 a potential biomarker of treatment response. Although motor improvement does not seem to 583 be CST-type dependent after bimanual training [12, 54], there are conflicting results 584 regarding unimanual training [55–57]. Furthermore, our results highlight the importance of 585 considering the sensory system together with the available motor execution paradigms during 586 UL training. Preliminary results of recent studies have shown the effectiveness of bimanual 587 and sensory training on both motor and sensory function in uCP [58, 59]. To further support 588 interventions targeting sensory deficits, there is evidence in healthy adults suggesting that 589 sensory input can modulate the excitability in both motor cortices simultaneously, as well as 590 the communication between hemispheres [60]. In this line, it seems relevant to combine 591 bimanual and sensory training to enhance the excitability of both motor cortices, which may 592 increase intra- and inter-hemispheric connections between the sensory and motor systems, 593 potentially resulting in long-lasting neuroplastic changes.

594 Next to the training approaches, it is also important to identify clinically feasible measures to 595 infer the CST wiring and the sensory system. As these assessments are not always pleasant in 596 young children nor practical in a clinical setting, there is a necessity to find tools that are 597 more applicable to daily practice than neurophysiological techniques. To probe the motor 598 system, mirror movements have been put forward as a valid clinical assessment tool that may 599 reflect the underlying individual CST wiring [9, 61]. On the other hand, it seems very 600 challenging to develop an accessible and simple tool to clinically probe the sensory system in 601 uCP. Further research in this field is required to develop quantitative and valid measures of 602 sensory function (e.g. perceptual threshold of touch with electrical stimulation [62] or robotic 603 measures of proprioception [49, 63]) and to link these measures to the underlying 604 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

612 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 613 614 normally higher in children and may be even higher in individuals with uCP. This limitation 615 might have prevented us from finding a CST projection to eventually diagnose the individual 616 as CST<sub>bilat</sub> or CST<sub>ipsi</sub> wiring. Furthermore, the MEP data were not analysed, which may 617 provide with useful insights in future studies. Lastly, although our sample size was large and 618 covers the most common lesion timing groups, our results cannot be completely extended to 619 those children with malformations or postnatally acquired brain injuries, as these were not 620 included in the analyses.

# 621 Conclusions

622 CST wiring mainly determines UL motor function, although also lesion extent and damage to 623 the basal ganglia and thalamus significantly contributed to the prediction of UL motor 624 deficits. For sensory function, lesion extent, timing, and the type of CST wiring pattern seem 625 to be important to develop adequate sensory function. The underlying CST wiring seems to 626 disrupt the association between sensory and motor function, pointing toward different 627 mechanisms of sensorimotor integration in uCP. The results of our study contribute to a 628 better understanding of the underlying pathophysiology of motor and sensory function and 629 highlight the importance of investigating sensorimotor integration in future studies. 630 Subsequently, these insights will aid in developing new intervention strategies tailored to the 631 specific deficits of the motor and sensory system of the individual child with uCP.

# 632 Data Availability

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

# 635 **Conflicts of Interest**

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

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#### 647 Supplementary materials

- Table 1. Descriptive information of the distribution of the lesion location and extent
- 649 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
- 653 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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