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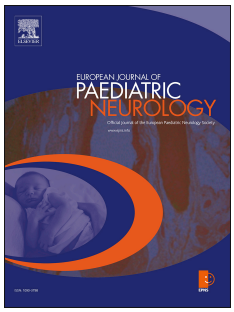

How does the interaction of presumed timing, location and extent of the underlying brain lesion relate to upper limb function in children with unilateral cerebral palsy?

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Title:

How does the interaction of presumed timing, location and extent of the underlying brain lesion relate to upper limb function in children with unilateral cerebral palsy?

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Abbreviations

sqMRI scale: semi-quantitative MRI scale

Abstract

Background: Upper limb (UL) function in children with unilateral cerebral palsy (CP) may vary largely depending on presumed timing, location and extent of brain lesions. These factors might exhibit a complex interaction and the combined prognostic value warrants further investigation. This study aimed to map lesion location and extent and assess whether these differ according to presumed lesion timing and to determine the impact of structural brain damage on UL function within different lesion timing groups.

Materials and methods: Seventy-three children with unilateral CP (mean age 10 years 2 months) were classified according to lesion timing: malformations (N=2), periventricular white matter (PWM, N=42) and cortical and deep grey matter (CDGM, N=29) lesions. Neuroanatomical damage was scored using a semi-quantitative MRI scale. UL function was assessed at the level of body function and activity level.

Results: CDGM lesions were more pronounced compared to PWM lesions (p=0.0003). Neuroanatomical scores were correlated with a higher degree to UL function in the CDGM group (r_s=-0.39 to r_s=-0.84) compared to the PWM group (r_{rb}=-0.42 to r_s=-0.61). Regression analysis found lesion location and extent to explain 75% and 65% (p<0.02) respectively, of the variance in AHA performance in the CDGM group, but only 24% and 12% (p<0.03) in the PWM group.

Conclusions: In the CDGM group, lesion location and extent seems to impact more on UL function compared to the PWM group. In children with PWM lesions, other factors like cortical reorganization and structural connectivity may play an additional role.

Key words:

upper extremity, cerebral palsy, magnetic resonance imaging, brain injury, rehabilitation

1. Introduction

Cerebral palsy (CP) is the most frequent cause of childhood disability in which a brain lesion causes motor dysfunction).[1] In children with unilateral CP, upper limb (UL) impairments such as spasticity, muscle weakness and sensory dysfunction result in activity limitations which are expressed in difficulties with grasping, releasing and manipulating objects.[2,3] The heterogeneity of these impairments and activity limitations is large,[3,4] and may strongly depend on the anatomical characterization of the underlying brain lesion, i.e. presumed timing, location and extent.[5–14]

Brain lesions in children with unilateral CP are often classified into three broad categories according to presumed lesion timing: cortical malformations (first and second trimester), periventricular white matter (PWM) lesions (from late second till early third trimester) and cortical and deep grey matter (CDGM) lesions (around term age).[1] Children with PWM lesions have higher chances of developing a better UL function than children with CDGM lesions.[5–12] Nevertheless, there is a large heterogeneity in severity of UL dysfunction within each of these groups.[7] A second possible neural correlate of UL function is lesion location.[7,9,10,12,13] Previous studies indicated that the UL is most impaired in case of damage of subcortical structures, such as the basal ganglia (BG),[7,9,12] thalamus[7,9,12] or the posterior limb of the internal capsule (PLIC)[10,13]. A third factor suggested to influence UL function is lesion extent. Three studies found that the severity of lesion extent was related with a more impaired UL.[8,9,13] Another study could not demonstrate that the degree of white matter loss contributed to the explanation of the variability in hand function.[14]

Although some evidence exists for the role of presumed timing, location and extent, these factors might exhibit a complex interaction while their combined prognostic value has not yet been investigated. Furthermore, the use of qualitative brain lesion classifications hinders the detailed mapping of lesions in children with CP. Recently, a visual semi-

quantitative scale was developed specifically for children with CP providing an in-depth assessment of structural brain damage (location and extent) on MRI (sqMRI scale).[13,15] The structure-function relationship was investigated in unilateral CP with PWM lesions using this scale, but only into limited extent in children with CDGM lesions.[13,16] Furthermore, there is a paucity of data on the difference in location and extent of brain lesions between different timing groups and on the combined impact of the three mentioned neurological factors on UL function assessed on the level of body function and activity.

The first objective of this study was to map brain lesion locations and extent in children with unilateral CP using the sqMRI scale by Fiori et al.[15], and to assess whether this differs between different timing groups. A second objective was to determine the relation between lesion location and extent and UL function for the different timing groups. The insights of these results might contribute to a better prediction of UL outcomes for the child and to a more individualized treatment planning.

2. Materials and Methods

2.1 Participants

Participants were recruited via the CP-care program of the University Hospitals Leuven. Children with a predominant spastic type of congenital unilateral CP were included if they were aged between 4-15 years, able to comprehend test instructions and had a brain MRI scan available. This scan included at least fluid-attenuated inversion recovery sequences, taken after the age of 3 years as described by Fiori et al.[15], to be able to score the brain lesion with the sqMRI scale. Children were excluded if they had a history of UL surgery or Botulinum toxin-A injections during the last six months prior to testing. The protocol was approved by the Ethical Committee of the University Hospitals Leuven and informed consent was obtained from the parents.

2.2 Procedure

Clinical assessments were performed at the Clinical Motion Analysis Laboratory of the University Hospitals Leuven using a standardized test protocol.[17] Children were assessed by three physiotherapists routinely involved in the clinical evaluation of children with CP. Each MRI was scored using the sqMRI scale[13,15] by one paediatric neurologist (EO) who was blinded to the clinical outcome. In case a child had multiple MRI scans available, the scan closest to the clinical assessment was chosen. In 22 children, the scan was performed at least one year before the UL clinical assessment, in 28 in the same year and in 23 children, the scan was taken at least one year after the UL clinical assessment. However, all children were included as structural brain damage is not expected to change after the age of three when the myelination process is completed.[18] All children were also classified according to their presumed lesion timing.[1] In case children had multiple lesions that could be assigned to more than one group; they were classified according to their predominant pattern taking into account their medical history.

2.3 Clinical assessment

General information such as age, sex, impaired side, Manual Ability Classification System (MACS)[19] and Gross Motor Function Classification System (GMFCS) were collected. At body function level, motor assessments included muscle tone, muscle strength and grip strength. Muscle tone was evaluated with the Modified Ashworth Scale[20] in eleven muscle groups at the level of the shoulder, elbow, wrist and hand (total score; 0-44). Muscle strength was determined using the ordinal rating scale of Daniels and Worthingham[21] in nine muscle groups at the level of the shoulder, elbow and wrist (total score; 0-45). Grip strength was measured with the Jamar dynamometer as the mean of three maximum contractions at each side. Grip strength ratio of the impaired hand to the non-impaired hand was calculated to eliminate the correlation between grip strength and age.[22,23] Sensory function was assessed by evaluating two-point discrimination (TPD) and stereognosis.[17] TPD was assessed with an

aesthesiometer® at the distal phalanx of the index finger. The minimal distance at which one or two points could correctly be distinguished was evaluated. Stereognosis was assessed by tactile identification of six objects. For more details see Klingels et al.[17] Interrater and test-retest reliability of this protocol has been established.[17]

At activity level, bimanual performance was assessed with the Assisting Hand Assessment (AHA).[24,25] This test evaluates how effectively the impaired hand is spontaneously used during bimanual activities in 22 items. Raw scores were converted to 0-100 logit-based AHA units. Unimanual capacity was assessed with the Melbourne Assessment of Unilateral Upper Limb function (MUUL)[26] and the Jebsen-Taylor Hand Function Test (JTHFT)[27,28]. The MUUL comprises 16 unimanual tasks. Raw scores were converted to a percentage score. During the JTHFT, the time needed to complete six functional tasks was recorded for the impaired hand. The ABILHAND-kids questionnaire,[29] filled in by the parents, assessed manual performance during daily activities. The raw sum score was converted to a logit measure. All clinical scales are found to be reliable and valid.[24–29]

2.4 Semi-quantitative MRI scale

The sqMRI scale[13,15] consists of a graphical black and white template of six axial slices and a simple scoring system. In a first step, the lesion was drawn onto the template. Afterwards, a score was calculated for the periventricular, middle and cortico-subcortical layers of the frontal, parietal, temporal and occipital lobe for both hemispheres separately. Each layer was scored for each lobe (0-1) resulting in a lobar score (0-3) and summed up to a hemispheric layer score (0-4). Subsequently, a global hemispheric score (0-12) could be calculated from the sum of each layer for the ipsilesional as well as contralesional hemisphere. Damage to BG (lenticular and caudate nucleus), PLIC, thalamus and brainstem

were scored directly from the MRI as either affected or non-affected (global subcortical score, 0-5). These five structures will hereafter be referred to as subcortical structures. Scores of the cerebellum and corpus callosum were left out due to the number of missing values. The ipsilesional and contralesional global total score (0-17) was calculated as the sum of the global hemispheric and global subcortical score of each respective hemisphere. Finally, the sum of all these scores led to the total lesion global score (0-40). High reliability and validity has been demonstrated.[13,15] A comprehensive description of the scale can be found in Fiori et al.[15]

Lesion location was defined as damage to the four lobes, three layers and five subcortical structures. Lesion extent was determined by the ipsilesional global hemispheric, ipsilesional global subcortical and ipsilesional global total scores.

2.5 Statistical analysis

Descriptive statistics were used to document general and clinical characteristics of the participants and to map location and extent of structural brain damage in the different timing groups. Differences in clinical outcome as well as in brain damage between the PWM and CDGM group were investigated. Children with malformations were excluded because of the small sample size (N=2). A paired t-test was used for normally distributed, continuous data or a Wilcoxon rank sum test in case of non-normally distributed and ordinal data. For the dichotomous scores of the scale, a Fisher Exact or Chi-Square test was used. Correlation coefficients were calculated between the scores of ipsilesional brain damage and all clinical outcomes of UL function for the PWM and CDGM group, using Spearman's rank (r_s), biserial (r_b), rank biserial (r_{rb}) or point biserial (r_{pb}) correlation coefficients depending on the type of data. Also correlations between AHA performance and contralesional global scores were calculated. Correlation coefficients <0.30 were considered as little or no correlation, 0.30 to

0.50 a low, 0.50 to 0.70 a moderate, >0.70 a high and 0.90 to 1.00 a very high correlation.[30] A Holm-Bonferroni correction was applied for multiple testing with α=0,05. Only correlations significant after correction will be discussed. Finally, a stepwise multiple regression analysis was used to identify which scores explained the variance in AHA performance for both groups based on lesion location and extent. For lesion location, the ipsilesional frontal, parietal and temporal lobe, periventricular and subcortical layer and all subcortical structures were entered in the regression model. For lesion extent, the ipsilesional global hemispheric and subcortical scores were used. Two-sided 5% level of significance was used. Statistical procedures were carried out with SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1 Participants

Seventy-three children (43 males, 30 females; 37 right-sided, 36 left-sided; MACS I=27, II=33, III=13; GMFCS I=61; II=12) with congenital unilateral CP were included in the study. Average age at time of clinical assessments was 10 years and 2 months (SD ± 2 years and 8 months), and at time of the MRI 10 years and 5 months (SD ± 3 years and 10 months). Two children had cortical malformations, 42 children presented with PWM lesions and 29 children were classified as CDGM lesions. For all body function and activity measures, children with CDGM lesions performed worse than children with PWM lesions ($p<0.003$), except for the ABILHAND-kids questionnaire ($p=0.06$) (see Table SF, supplementary files).

3.2 Lesion characteristics in different timing groups

In the *PWM group*, the frontal and parietal ipsilesional lobes were involved in more than 80% of the children, while the temporal and occipital lobes were affected in half of the

children (see Figure 1A). The periventricular and middle white matter layer were affected in almost all children, whereas the cortico-subcortical layer was damaged in only 25% of the children. Remarkably, 75% of the children had damage to at least one subcortical structure. The PLIC was most commonly affected (62%) and also thalamus and brainstem were often involved (43% and 52% respectively) (see Figure 1A). In the CDGM group, 70% of the children showed damage in all lobes, 80% in all layers, and 75% in all subcortical structures with only the caudate nucleus less frequently damaged (52%) (see Figure 1A).

Contralesional damage was seen in 52% and 34% of the children with PWM and CDGM lesions respectively (see Figure 1B). In the PWM group, contralesional damage was most often seen in the frontal lobe (38%). The other lobes were damaged in 17% to 29% of the children with PWM lesions. In the CDGM group, contralesional damage was more equally distributed across the lobes in about 25% of the children for each lobe. In both groups, the periventricular and middle white matter layer were most often affected (PWM, 45% and 43%; CDGM, 35% and 31% respectively). Only one child with PWM lesions showed damage in the contralesional cortico-subcortical layer. Also in the CDGM group, this layer was less frequently affected (10%). Damage to contralesional subcortical structures was rare in both groups.

Table 1 shows the statistical comparison of the ipsilesional scores between the PWM and CDGM group. For lesion location, damage to the frontal, parietal and temporal lobe, the middle white matter and cortico-subcortical layer ($p<0.001$), was significantly more often seen in the CDGM group compared to the PWM group. Also damage to the lenticular nucleus, caudate nucleus and thalamus was more frequent in children with CDGM lesions ($p<0.001$). For lesion extent, all global scores were also significantly higher in the CDGM group ($p<0.0004$).

3.3 Relation between lesion characteristics and upper limb function in different timing groups

3.3.1 Sensorimotor outcome

Correlation analysis between lesion characteristics and motor function in the *PWM group* revealed only a few significant correlations (see Table 2A). Low significant correlations were found for muscle tone with damage to the PLIC and thalamus (r_{rb}=0.46 and r_{rb}=0.46) and one moderate correlation with the global subcortical score (r_s=0.52). No significant correlations were found for muscle strength and grip strength. A higher number of significant correlations was found with sensory outcome. Correlation coefficients for 2PD were low, except for a moderate correlation with the global subcortical score (r_s=-0.50). For stereognosis, mainly moderate correlations were found with all subcortical structures (r_{rb}=-0.43 to r_{rb}=-0.58), except for the brainstem. Stereognosis was also moderately correlated with the ipsilesional global subcortical and ipsilesional global total score (r_s=-0.61 and r_s=-0.50 respectively).

Correlation analysis between lesion characteristics and motor function in the *CDGM group* (see Table 2B) revealed a much higher number of significant correlations. Muscle tone correlated highly with damage to the parietal lobe, PLIC and thalamus (r_s=0.70 to r_{rb}= 0.76). For muscle strength, high correlations were found with damage to the frontal and parietal lobes and the middle white matter layer, along with the ipsilesional global total score (r_s=-0.70 to r_s=-0.79). For grip strength, high correlations were found with damage to the PLIC (r_{rb}=-0.77) and thalamus (r_{rb}=-0.77). Furthermore, moderate correlations were found for 2PD with all scores (r_{rb}=-0.46 to r_s=-0.62), except for the temporal and occipital lobe, periventricular white matter layer and lenticular nucleus. For stereognosis, low correlations were found with damage to the lenticular nucleus, PLIC and thalamus, along with the ipsilesional global subcortical and ipsilesional global total score (r_{rb}=-0.40 to r_{rb}=-0.48).

3.3.2 Activity outcome

For all activity measures, only few and low correlations were found in the *PWM group*. (see Table 2A) The AHA and MUUL correlated significantly with damage to thalamus (r_{pb}=-0.44 and r_{rb}=-0.42 respectively). The AHA was further correlated with damage to the PLIC (r_{pb}=-0.49) and the MUUL with the global subcortical score (r_s=-0.48). The JTHFT and ABILHAND-kids questionnaire were not significantly correlated with structural brain damage in this group. In the *CDGM group*, significant correlations were found between all neuroanatomical scores and all activity measures (see Table 2B). Overall, highest correlations were found with the AHA, while for the ABILHAND-kids questionnaire correlations were mainly moderate. For the AHA, high correlations were found with damage to the frontal and temporal lobe, all three layers, PLIC, thalamus and brainstem, along with all global scores (r_{pb}=-0.70 and r_b=-0.84). The MUUL was highly correlated with damage to the frontal lobe, middle white matter and cortico-subcortical layer, PLIC and thalamus, along with the ipsilesional global total score (r_s=-0.70 to r_s=-0.79). For the JTHFT, high correlations were found with damage to the frontal lobe, PLIC and thalamus (r_{rb}=0.72 to r_s=0.74). The ABILHAND-kids questionnaire correlated highly with damage to the middle white matter layer.

Finally, correlations between contralesional damage and AHA scores were explored in both groups. For both groups, there were no significant correlations between AHA performance and all contralesional global scores (p>0.14).

3.4 Regression analysis of bimanual performance

Regression analysis based on lesion location revealed the PLIC as the only significant predictor in the PWM group explaining 24% of the variance in AHA performance (p=0.001). For the CDGM group, the total amount of explained variance in AHA performance was 75%,

with the temporal lobe as the strongest contributor (R^2=0.69, p=0.02). The frontal lobe further contributed significantly to the explained variance (R^2=0.06, p=0.05).

For lesion extent, only 12% of the variance was explained by the global subcortical score (p=0.03) in the PWM group. For the CDGM group, the global hemispheric score explained 65% of the variance in AHA performance (p<0.0001).

4. Discussion

To the best of our knowledge, this is the first study that examined the impact of the interaction of presumed lesion timing, location and extent on UL function using a comprehensive assessment at the level of body function and activity in a large representative sample of children with congenital unilateral CP. The first aim was to map brain lesions and investigate whether location and extent differed according to presumed lesion timing. Regarding location, the PLIC and brainstem were equally damaged in both groups. Further, all lobes and the middle white matter and cortico-subcortical layer as well as the thalamus and the lenticular and caudate nucleus were more often damaged in children with CDGM lesions. Regarding lesion extent, all global scores were significantly higher in the CDGM group compared to the PWM group. Hence, these results indicate that CDGM lesions are more extended than PWM lesions, which is in line with the study of Scheck et al.[11] They quantified lesion volume using voxel-based morphometry and showed that cortical involvement is more pronounced in children with CDGM lesions.

The second aim was to assess the relation between lesion location and extent with UL function and to investigate whether this differed between timing groups. Strikingly, more significant and higher correlations were found for motor and sensory function with all neuroanatomical scores in the CDGM group compared to the PWM group displaying fewer and lower correlations. In the PWM group, mostly damage to the PLIC and thalamus was

related with UL motor function. In the CDGM group, correlations with these same brain structures were revealed, although correlation coefficients were much higher. The PLIC and thalamus are known for their important roles in processing sensorimotor signals.[12,31] The PLIC entails motor pathways, while all sensory information first passes through the thalamus before reaching the cortex. The importance of the integrity of these structures for UL function independent of lesion timing is in line with previous studies.[7,9,10,12,13] In addition, regression analysis revealed the PLIC as a significant predictor to explain AHA performance in the PWM group, which emphasizes the importance of this structure for UL function.

Regression analysis further highlighted the differential impact of lesion location on UL function between both groups. In the PWM group, only 24% of the variance in AHA performance could be explained by lesion location in contrast to 75% in the CDGM group. Pagnozzi et al. also revealed a clearly higher explained variance in AHA performance in the CDGM group compared to the PWM group.[16]

Furthermore, lesion extent also seems to impact far more on UL motor function in children with CDGM lesions. In the CDGM group, we found significantly high correlations between UL motor function and all global scores. Additionally, 65% of the variance in AHA performance was explained by the ipsilesional global hemispheric score. Oppositely, in the PWM group, only 12% of the variance in AHA performance could be explained by the global subcortical score, which was the only global score that correlated significantly with UL motor function. Fiori et al. also found no correlation between the global hemispheric score and UL activity measures in children with PWM lesions.[13]

In summary, our findings demonstrate that structural brain damage is a major determinant of UL function in children with CDGM lesions. The fewer and low correlations as well as low explained variance show that this is much less the case for children with PWM lesions. This indicates that other factors may be more important in understanding UL function

in the PWM group. In these children, the use of other imaging modalities might further clarify the relation between brain lesion characteristics and UL function. Diffusion tensor imaging (DTI) is a more recent imaging technique that has been suggested to be superior to structural MRI in detecting more subtle brain abnormalities in white matter.[32] Additionally, DTI parameters have already been proven to relate to UL function in children with unilateral CP.[14,31] Thus, DTI might be a complementary neuroimaging technique in future studies for children with PWM lesions. The type of cortical reorganization may also be of further importance which can be documented with the use of transcranial magnetic stimulation (TMS). It has been shown that children with PWM lesions have a higher potential for contralesional reorganization than children with CDGM lesions, which is known to impact on UL function.[8,33,34] Consequently, we hypothesize that the type of reorganization and structural connectivity is more important in determining UL function than structural brain damage based on MRI images in children with PWM lesions as has been recently described by Jaspers et al.[12] However, DTI also has limitations that need to be considered, such as being less accurate in areas of crossing, kissing and fanning fibers[35] and its difficulty to apply in children with large lesions. In addition, TMS cannot be applied in children with epilepsy. Moreover, a structural MRI is still considered the gold standard to underpin the clinical presentation and thus, corroborate the diagnosis of CP.[36] Our results further confirm that the sqMRI scale can be easily used to describe location and extent of brain lesions in more detail in children with unilateral CP. Secondly, we found evidence that this scale is suited for providing prognostic information about UL function, but mainly in children with CDGM lesions. In addition, automatization of the scale would further enhance its clinical utility.[37]

Another interesting finding in the PWM group was the more pronounced association with sensory outcome compared to motor outcome. However, significant low to moderate correlations were found with damage to solely subcortical structures. This might be explained

by the fact that sensory pathways reach their cortical destination sites only at the beginning of the third trimester of pregnancy and may thus still bypass the lesion.[38,39] This may offer an explanation of why correlations with cortical structures such as the parietal lobe, which encompasses the primary and secondary somatosensory cortex were lacking in children with PWM lesions. In the CDGM group, 2PD was correlated with damage to the frontal and parietal lobe. In these children, sensory pathways already reached their cortical destination sites when the lesion occurs. Damage to the frontal and parietal lobes may thus impact more on sensory outcome in this group. The caudate nucleus showed highest correlations with sensory outcome in both groups. Brain activation of the caudate nucleus has been demonstrated during 2DP and decision-making tasks.[40,41] Fiori et al. also found that the caudate nucleus contributed significantly to the variation in 2PD in children with PWM lesions.[13] Overall, only low to moderate correlations were found between sensory outcomes and structural brain damage in contrast to motor outcomes. This might imply that the integrity of structural and/or functional connectivity between multiple brain areas is more important for these sensory functions than structural brain damage. Bleyenheuft et al.[42] indeed reported a very high correlation between structural integrity of motor pathways and stereognosis. However, Tsao et al.[43,44] only found low correlations between structural connectivity of motor and sensory pathways with both stereognosis and 2PD. Little is known on the functional connectivity of sensory pathways. Papadelis et al. suggested an impaired somatosensory processing network in children with spastic CP.[45] Furthermore, functional MRI studies in healthy adults revealed complex neural networks during the evaluation of stereognosis and 2PD.[41,46] Further study is needed on the combined impact of structural and functional connectivity on sensory function in children with unilateral CP which might further elucidate the relationship between brain damage and UL sensory outcomes.

Despite the fact that clinical impairments were clearly unilateral, bilateral lesions were seen in 52% and 34% of children with PWM and CDGM lesions respectively. Contralesional damage was mainly found in the cortical areas and was rare in the cortico-subcortical layer and subcortical structures. Bilateral brain damage in children with unilateral CP has been previously reported although frequencies were highly variable.[6–8,10] Correlations between the contralesional global scores and AHA performance were not significant for both groups. This is in line with Holmefur et al,[9] who already reported the lack of impact of bilateral abnormalities on UL function.

This study also warrants some critical reflections. Due to the small number of children with malformations (N=2), no conclusions can be made for this group. A further lack is that we could not describe the impact of damage to the corpus callosum and cerebellum due to the exclusion of these structures. However, both the corpus callosum and cerebellum have recently been shown to relate to bimanual function[47] and manual dexterity[48] respectively. Hence, both structures need to be considered in future studies. Moreover, the functional evaluation and MRI-scan were not always performed at the same age. The average age gap included 2 years and 4 months (± 2 years 4 months). However, there was no significant difference regarding this time gap between the PWM and CDGM group (p=0.14). Furthermore, structural brain damage, visualized on MRI, is not expected to change after the age of three when the myelination process is completed.[18] Finally, it must be acknowledged that the scoring system of the sqMRI scale also has some limitations as it remains a semi-quantitative assessment. Nevertheless, a high degree of reliability of the scale has been demonstrated as well as validity in children with PWM lesions.[13,15] This study further established the validity of the sqMRI scale in children with CDGM lesions and proved its clinical utility in this target group.

5. Conclusion

Information on lesion location and extent from a sqMRI scale combined with the knowledge of lesion timing provides important prognostic information, especially in children with CDGM lesions. PWM lesions on the other hand, are associated with less brain damage and are less related to UL function. Cortical reorganization and structural connectivity may play an additional role in the clinical outcome in these children. This knowledge undoubtedly contributes to a better prediction of UL function for children with congenital unilateral CP and opens perspectives for individually tailored rehabilitation.

Conflict of Interest Statement

The Author(s) declare(s) that there is no conflict of interest' with respect to the research, authorship, and/or publication of this article.

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Figure 1. Percentage of ipsilesional (A) and contralesional (B) damage in the PWM and CDGM group. Abbreviations: PWMD, periventricular white matter; CDGM, cortical and deep grey matter; F, frontal lobe; P, parietal lobe; T, temporal lobe; O, occipital lobe; PV, periventricular layer; M, middle white matter layer; SC, subcortical layer; NL, lenticular nucleus; NC, caudate nucleus; PLIC, posterior limb of the internal capsule; TH, thalamus; BS, brainstem; *, significant after Holm-Bonferroni correction α=0.05

Table 1. Descriptive statistics and comparison of the ipsilesional scores between the periventricular white matter and cortical and deep grey matter lesions

		PWM (N=42)	CDGM (N=28)	P-value
Ipsilesional lobes				
F tot (0-3) [a]	Me (P25-P75)	1 (1-1.5)	2.5 (1.0-3.0)	0.001*
P tot (0-3) [a]	Me (P25-P75)	1.5 (1-2)	3.0 (2.0-3.0)	0.0002*
T tot (0-3) [a]	Me (P25-P75)	0.5 (0-1.5)	3.0 (1.0-3.0)	<0.0001*
O tot (0-3) [a]	Me (P25-P75)	0.25 (0-1.5)	1.0 (0.0-2.0)	0.04
Ipsilesional hemispheric layers				
PV (0-4) [a]	Me (P25-P75)	2.25 (1.5-3.0)	3.5 (2.0-4.0)	0.07
M (0-4) [a]	Me (P25-P75)	1.5 (1.0-2.0)	3.0 (1.5-3.5)	0.0003*
SC (0-4) [a]	Me (P25-P75)	0.0 (0.0-0.5)	2.5 (1.0-3.0)	<0.0001*
Global (0-12) [a]	Me (P25-P75)	3.25 (2.5-5)	9.0 (5.5-10.5)	0.0004*
Ipsilesional SS				
Lenticular nc (0-1) [b]				<0.0001*
Intact	N (%)	30 (71%)	6 (21%)	
Damaged	N (%)	12 (29%)	23 (79%)	
Caudate nc (0-1) [b]				0.002*
Intact	N (%)	36 (86%)	15 (52%)	
Damaged	N (%)	6 (14%)	14 (48%)	
PLIC (0-1) [b]				0.7
Intact	N (%)	16 (38%)	5 (17%)	
Damaged	N (%)	26 (62%)	24 (83%)	
Thalamus (0-1) [b]				0.001*
Intact	N (%)	24 (57%)	5 (17%)	
Damaged	N (%)	18 (43%)	24 (83%)	
Brainstem (0-1) [b]				0.14
Intact	N (%)	20 (48%)	8 (28%)	
Damaged	N (%)	22 (52%)	21 (72%)	
Global (0-5) [a]	Me (P25-P75)	2.0 (1.0-3.0)	4.0 (3.0-5.0)	0.0003*
Ipsilesional total				
Global (0-17) [a]	Me (P25-P75)	5.0 (4.0-7.0)	13.5 (9.0-15.0)	0.0003*

Abbreviations: Me, median; P, percentile; N, number of children; F, frontal lobe; P, parietal lobe; T, temporal lobe; O, occipital lobe; PV, periventricular layer; M, middle white matter layer; SC, cortico-subcortical layer; nc, nucleus; PLIC, posterior limb of the capsula interna; SS, subcortical structures; [a], Wilcoxon rank sum test; [b], Fisher's exact test; PWM, periventricular white matter; CDGM, cortical and deep grey matter; *significant after Holm-Bonferroni correction α=0.05

Table 2: Correlations between ipsilesional scores and clinical outcome for the PWM (2A) and CDGM group (2B)

Table 2A: PWM group (N=42)

	Muscle tone	Muscle strength	Grip strength	TPD	Stereognosis	AHA	MUUL	JTHFT	ABILHAND -kids
Ipsilesional lobes									
F tot (0-3)	r_s= 0.36	r_s= -0.33	r_s= -0.18	r_s= -0.31	r_s= -0.28	r_b= -0.28	r_s= -0.28	r_s= 0.43	r_s= -0.35
P tot (0-3)	r_s= -0.01	r_s= 0.04	r_s= 0.09	r_s= -0.28	r_s= -0.11	r_b= 0.12	r_s= 0.07	r_s= 0.03	r_s= -0.23
T tot (0-3)	r_s= 0.06	r_s= -0.06	r_s= 0.09	r_s= -0.34	r_s= -0.39	r_b= 0.14	r_s= 0.00	r_s= 0.07	r_s= 0.03
O tot (0-3)	r_s= 0.21	r_s= -0.10	r_s= -0.03	r_s= -0.28	r_s= -0.31	r_b= 0.02	r_s= -0.17	r_s= 0.13	r_s= -0.04
Ipsilesional hemispheric layers									
PV (0-4)	r_s= 0.04	r_s= -0.10	r_s= 0.05	r_s= -0.37	r_s= -0.36	r_b= 0.15	r_s= -0.01	r_s= 0.07	r_s= -0.01
M (0-4)	r_s= 0.12	r_s= -0.07	r_s= 0.08	r_s= -0.26	r_s= -0.36	r_b= 0.05	r_s= -0.02	r_s= 0.09	r_s= -0.19
SC (0-4)	r_s= 0.39	r_s= -0.21	r_s= -0.07	**r_s= -0.45***	r_s= -0.31	r_b= -0.14	r_s= -0.18	r_s= 0.28	r_s= -0.33
Global (0-12)	r_s= 0.08	r_s= -0.14	r_s= 0.09	r_s= -0.38	r_s= -0.39	r_b= 0.07	r_s= 0.01	r_s= 0.08	r_s= -0.09
Ipsilesional SS									
Lenticular nc (0-1)	r_{rb}= 0.23	r_{rb}= -0.13	r_{rb}= -0.07	r_{rb}= -0.24	**r_{rb}= -0.53***	r_{pb}= -0.21	r_{rb}= -0.27	r_{rb}= 0.27	r_{rb}= -0.19
Caudate nc (0-1)	r_{rb}= 0.03	r_{rb}= -0.01	r_{rb}= -0.21	**r_{rb}= -0.47***	**r_{rb}= -0.58***	r_{pb}= -0.05	r_{rb}= -0.12	r_{rb}= 0.03	r_{rb}= -0.07
PLIC (0-1)	**r_{rb}= 0.46***	r_{rb}= -0.19	r_{rb}= -0.34	**r_{rb}= -0.44***	**r_{rb}= -0.43***	**r_{pb}= -0.49***	r_{rb}= -0.32	r_{rb}= 0.17	r_{rb}= -0.03
Thalamus (0-1)	**r_{rb}= 0.46***	r_{rb}= -0.37	r_{rb}= -0.28	r_{rb}= -0.35	**r_{rb}= -0.50***	**r_{pb}= -0.44***	**r_{rb}= -0.42***	r_{rb}= 0.30	r_{rb}= -0.31
Brainstem (0-1)	r_{rb}= 0.32	r_{rb}= -0.15	r_{rb}= -0.19	r_{rb}= -0.31	r_{rb}= -0.32	r_{pb}= -0.09	r_{rb}= -0.06	r_{rb}= 0.08	r_{rb}= -0.01
Global (0-5)	**r_s= 0.52***	r_s= -0.41	r_s= -0.27	**r_s= -0.50***	**r_s= -0.61***	r_b= -0.35	**r_s= -0.48***	r_s= 0.41	r_s= -0.18
Ipsilesional total									
Global (0-17)	r_s= 0.29	r_s= -0.30	r_s= -0.02	**r_s= -0.44***	**r_s= -0.56***	r_b= -0.12	r_s= -0.22	r_s= 0.25	r_s= -0.09

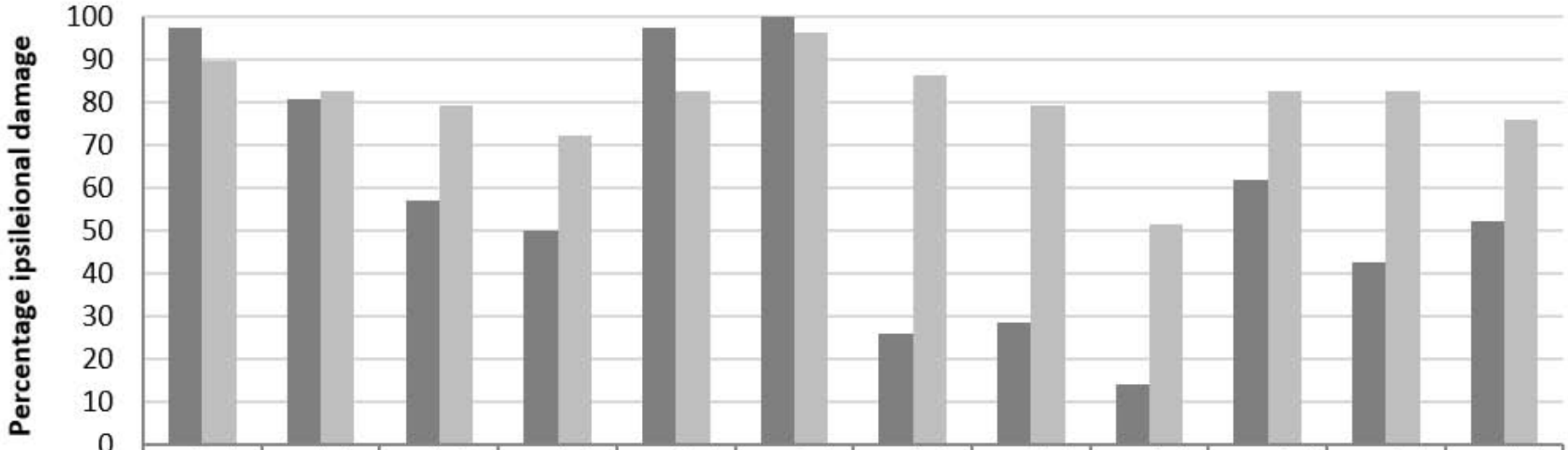
Abbreviations: PWM, periventricular white matter; CDGM, cortical and deep grey matter; F, frontal; P, parietal, T, temporal; O, occipital; PV, periventricular layer; M, middle white matter layer; SC, cortico-subcortical layer; nc, nucleus; PLIC, posterior limb of the internal capsule; SS, subcortical structures; BS, brainstem; TPD, two-point discrimination; AHA, Assisting Hand Assessment; MUUL, Melbourne Assessment of Unilateral Upper Limb Function; JTHFT, Jebsen-Taylor Hand Function Test; r_s, spearman rank; r_b, biserial; r_{pb}, point biserial; r_{rb}, rank biserial; * and bold, significant after Holm-Bonferroni correction α=0.05

Table 2B: CDGM group (N=29)

	Muscle tone	Muscle strength	Grip strength	TPD	Stereognosis	AHA	MUUL	JTHFT	ABILHAND -Kids
Ipsilesional lobes									
F tot (0-3)	**r_s= 0.59***	**r_s= -0.79***	r_s= -0.42	**r_s= -0.62***	r_s= -0.25	**r_b= -0.81***	**r_s= -0.79***	**r_s= 0.74***	**r_s= -0.58***
P tot (0-3)	**r_s= 0.70***	**r_s= -0.70***	r_s= -0.41	**r_s= -0.53***	r_s= -0.38	**r_b= -0.65***	**r_s= -0.51***	r_s= 0.47	**r_s= -0.54***
T tot (0-3)	**r_s= 0.65***	**r_s= -0.58***	**r_s= -0.54***	r_s= -0.45	r_s= -0.25	**r_b= -0.84***	**r_s= -0.65***	**r_s= 0.65***	**r_s= -0.69***
O tot (0-3)	**r_s= 0.58***	**r_s= -0.53***	r_s= -0.48	r_s= -0.30	r_s= -0.22	r_b= -0.49	**r_s= -0.53***	r_s= 0.38	**r_s= -0.53***
Ipsilesional hemispheric layers									
PV (0-4)	**r_s= 0.61***	**r_s= -0.64***	r_s= -0.39	r_s= -0.50	r_s= -0.23	**r_b= -0.75***	**r_s= -0.58***	r_s= 0.43	**r_s= -0.57***
M (0-4)	**r_s= 0.68***	**r_s= -0.74***	**r_s= -0.64***	**r_s= -0.57***	r_s= -0.38	**r_b= -0.76***	**r_s= -0.71***	**r_s= 0.61***	**r_s= -0.70***
SC (0-4)	**r_s= 0.69***	**r_s= -0.66***	**r_s= -0.59***	**r_s= -0.53***	r_s= -0.33	**r_b= -0.77***	**r_s= -0.70***	**r_s= 0.59***	**r_s= -0.67***
Global (0-12)	**r_s= 0.69***	**r_s= -0.69***	**r_s= -0.57***	**r_s= -0.55***	r_s= -0.31	**r_b= -0.81***	**r_s= -0.69***	**r_s= 0.57***	**r_s= -0.66***
Ipsilesional SS									
Lenticular nc (0-1)	**r_{rb}= 0.53***	**r_{rb}= -0.53***	**r_{rb}= -0.52***	r_{rb}= -0.32	**r_{rb}= -0.48***	**r_{pb}= -0.51***	**r_{rb}= -0.60***	**r_{rb}= 0.67***	**r_{rb}= -0.58***
Caudate nc (0-1)	r_{rb}= 0.42	r_{rb}= -0.47	r_{rb}= -0.43	**r_{rb}= -0.58***	r_{rb}= -0.46	r_{pb}= -0.51	**r_{rb}= -0.57***	**r_{rb}= 0.64***	r_{rb}= -0.40
PLIC (0-1)	**r_{rb}= 0.76***	**r_{rb}= -0.68***	**r_{rb}= -0.77***	**r_{rb}= -0.53***	**r_{rb}= -0.40***	**r_{pb}= -0.78***	**r_{rb}= -0.75***	**r_{rb}= 0.72***	**r_{rb}= -0.64***
Thalamus (0-1)	**r_{rb}= 0.76***	**r_{rb}= -0.68***	**r_{rb}= -0.77***	**r_{rb}= -0.53***	**r_{rb}= -0.40***	**r_{pb}= -0.78***	**r_{rb}= -0.75***	**r_{rb}= 0.72***	**r_{rb}= -0.64***
Brainstem (0-1)	**r_{rb}= 0.63***	**r_{rb}= -0.56***	**r_{rb}= -0.66***	**r_{rb}= -0.46***	r_{rb}= -0.13	**r_{pb}= -0.70***	**r_{rb}= -0.67***	**r_{rb}= 0.59***	**r_{rb}= -0.58***
Global (0-5)	**r_s= 0.54***	**r_s= -0.61***	**r_s= -0.54***	**r_s= -0.60***	**r_s= -0.45***	**r_b= -0.77***	**r_s= -0.66***	**r_s= 0.72***	**r_s= -0.49***
Ipsilesional total									
Global (0-17)	**r_s= 0.67***	**r_s= -0.72***	**r_s= -0.59***	**r_s= -0.61***	**r_s= -0.39***	**r_b= -0.83***	**r_s= -0.70***	**r_s= 0.60***	**r_s= -0.53***

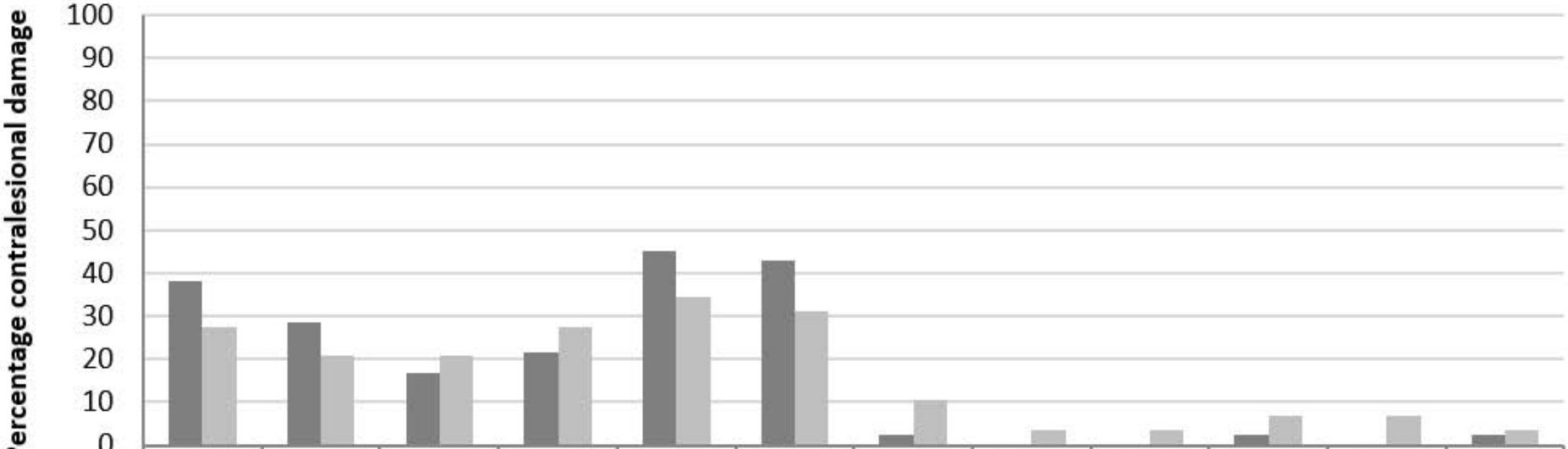
Abbreviations: CDGM, cortical and deep grey matter; F, frontal; P, parietal, T, temporal; O, occipital; PV, periventricular layer; M, middle white matter layer; SC, cortico-subcortical layer; nc, nucleus; PLIC, posterior limb of the internal capsule; SS, subcortical structures; BS, brainstem; TPD, two-point discrimination; AHA, Assisting Hand Assessment; MUUL, Melbourne Assessment of Unilateral Upper Limb Function; JTHFT, Jebsen-Taylor Hand Function Test; r_s, spearman rank; r_b, biserial; r_{pb}, point biserial; r_{rb}, rank biserial; * and bold, significant after Holm-Bonferroni correction α=0.05

A



	F (%)	P (%)	T (%)	O (%)	PV (%)	M (%)	SC (%)	NL (%)	NC (%)	PLIC (%)	TH (%)	BS (%)
PWM group	98	81	57	50	98	100	26	29	14	62	43	52
CDGM group	90	83	79	72	83	97	86	79	52	83	83	76

B



	F (%)	P (%)	T (%)	O (%)	PV (%)	M (%)	SC (%)	NL (%)	NC (%)	PLIC (%)	TH (%)	BS (%)
PWM group	38	29	17	21	45	43	2	0	0	2	0	2
CDGM group	28	21	21	28	34	31	10	3	3	7	7	3

Highlights

- PWM lesions have less structural brain damage compared to CDGM lesions
- Lesion location and extent are more strongly related to UL function in CDGM lesions
- The sqMRI scale is clinically useful, in particular in children with CDGM lesions