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Do mirror movements relate to hand function and timing of the brain lesion in children with unilateral cerebral palsy?

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Abstract

Aim: This study aimed to systematically map the severity of mirror movements (MM) in both hands in a prospective cohort of children with unilateral cerebral palsy (CP), and to explore the relationship with hand function and brain lesion type.

Method: Seventy-eight children were included (age 9y 4m ± 3y 1m, range 5–15y; 41 boys). MM were scored during three repetitive tasks following Woods and Teuber criteria. Strength, tone, Melbourne Assessment, Jebsen-Taylor test and Assisting Hand Assessment were evaluated. Lesions were classified into malformations (N=5), periventricular (N=43), cortico-subcortical (N=22), and postnatally acquired lesions (N=8).

Results: Significantly more MM were observed in the non-paretic versus the paretic hand ($p \leq 0.003$). Higher MM-scores in the *non-paretic hand* significantly correlated with lower distal strength and lower scores on unimanual and bimanual assessments (r=0.29–0.41). In the *paretic hand*, significant differences were found between lesion types (p=0.03).

Interpretation: The occurrence of MM in the non-paretic hand seems related to hand function, while MM in the paretic hand seem more related to the lesion timing, whereby children with earlier lesions present with more MM.

Short title

Mirror movements in unilateral cerebral palsy

What this paper adds

- More mirror movements are observed in the non-paretic versus the paretic hand.
- Poor hand function correlates with more mirror movements in the non-paretic hand.
- Mirror movements in the paretic hand are related to the brain lesion type.

Introduction

Children with unilateral cerebral palsy (CP) often experience difficulties in bimanual coordination, impacting upon daily life activities. Apart from spasticity, muscle weakness and sensory deficits, the occurrence of mirror movements (MM) has also been suggested as a possible contributing factor that interferes with bimanual performance.[1]

MM are described as 'involuntary movements of one body part that mirror the voluntary movement of the contralateral homologous body part'.[2,3] They are mainly observed in the upper limbs, symmetrical by nature, and their intensity increases with increasing task complexity or fatigue.[4,5] Physiological MM are present in newborns, show a steep decrease between 5 and 8 years of age, and disappear after 10 years of age.[4,6] These MM are most likely caused by incomplete maturation of the corpus callosum and concurrent less effective interhemispheric inhibition. Unilateral tasks thereby invoke activation of bilateral motor cortices.[6-8] Further maturation of the transcallosal pathways with age ensures increasing inhibition of the motor cortex ipsilateral to the task hand, thus reducing the occurrence of MM.[7]

MM have frequently been described in unilateral CP,[3,8,9] mostly in the non-paretic hand, albeit with large variability.[1,3,8-10] The pathogenesis for their occurrence is not yet fully understood. One potential hypothesis could be the activation of bilateral primary motor cortices due to deficient interhemispheric inhibition caused by the underlying brain lesion.[2,6] Conversely, the persistence of ipsilateral corticospinal projections between the non-lesioned motor cortex and the paretic hand has also been proposed as a possible mechanism for MM.[9-12] This reorganization of the corticospinal tract (CST) is unique in children with unilateral CP, and depends on both the timing and extent of the lesion.[9,13] The importance of lesion timing is further supported by the fact that children with congenital unilateral CP show more MM compared to those suffering from childhood stroke.[3,13] However, the exact link between lesion type and MM has not yet been investigated in a larger sample.

Moreover, little is known about the relationship between MM and upper limb function. MM have generally been associated with more severe impairments,[10,13] though only one study investigated this in more detail.[1] These authors found no relationship between the occurrence of MM in either hand and spasticity, muscle weakness or impaired dexterity. They did report an important relationship with bimanual skills.[1] However, this study was based on a small sample and lacked standardized testing. Further study using reliable and valid upper limb assessments is required to better understand the impact of MM on upper limb function.

The first aim of this study was to systematically map the occurrence and severity of MM in the paretic and non-paretic side during repetitive hand movements in a large sample of children with unilateral CP. Secondly, we aimed to define the relationship between MM and upper limb function and the role of brain lesion type regarding the occurrence of MM.

Methods

Participants

Children with unilateral CP, aged 5-15 years and with available brain MRIs were recruited consecutively from the University Hospital Pellenberg, Belgium between 2008 and 2013. Children with upper limb botulinum toxin-A injections within 6 months prior to testing or previous upper limb surgery, and children not mentally capable of cooperating with the assessments were excluded. The Ethical Committee of the University Hospital Leuven approved the protocol and all parents provided written informed consent.

Clinical assessments

Two trained physiotherapists, blind to the MRI findings, evaluated all children. Functional hand use was classified using the Manual Ability Classification System (MACS).[14]

Mirror movements (MM) were videotaped during three unimanual tasks: (1) fist opening and clenching, (2) finger opposition (thumb sequentially touches other four digits), and (3) finger tapping (fingers are sequentially lifted from the table surface).[1] Children were seated at a height adjustable table, elbows and forearms supported. Each task was executed five times, first with the non-paretic side. To optimize visibility of the hand movements, the video camera was placed orthogonally to the table surface. The occurrence of MM in the opposite hand was scored for each task following the Woods and Teuber criteria (total score 0-12): 0, no clear imitative movement; 1, barely discernable repetitive movements; 2, slight MM or stronger, but briefer repetitive movements; 3, strong and sustained repetitive movements; 4, movements equal to those expected for the intended hand.[5] Videos were scored by a third physiotherapist, who was blind to the child's clinical examination and MRI findings. Interrater and intra-rater reliability of the scoring of the MM was assessed using the ICC(2,1), with intraclass correlation coefficients > 0.82 ((Table SI, online supporting information).

At the ***body function level***, motor impairments were assessed using a standardized and reliable protocol.[15] *Muscle tone* was scored with the Modified Ashworth Scale at the forearm (pronators; range 0–4) and wrist (wrist/finger flexors; range 0-8). *Muscle strength* was evaluated according to the Medical Research Council rating at the forearm (supinators/pronators; range 0-10) and wrist (flexors/extensors; range 0-10). *Grip strength* was assessed with the Jamar dynamometer® as the mean of three maximum contractions. The ratio of the paretic versus the non-paretic hand was used for further analysis.

At the ***activity level***, the Melbourne Assessment of Unilateral Upper Limb Function[16] and the Jebsen-Taylor test[17] were used to evaluate *unimanual capacity*. The Melbourne Assessment measures quality of movement during 16 unimanual tasks (total raw score between 0 and 122, converted to percentages). The Jebsen-Taylor test provides a measure of manual dexterity by recording the movement time (seconds) required to perform six unimanual tasks, with a total maximum of 720 seconds. *Bimanual performance* was assessed with the Assisting Hand Assessment (AHA).[18] The AHA evaluates the spontaneous use of the paretic hand during bimanual play. Raw scores were converted to logit-based 0 to 100 AHA-units. High levels of reliability and validity were established for all activity assessments.[16,18,19]

Classification of brain lesions

MRI data were acquired using a 1.5T or 3T Philips Ingenia scanner (Philips Healthcare, Best, The Netherlands), and T1 (MPRAGE), T2 and/or FLAIR images were used for lesion classification. Congenital unilateral CP was defined as a unilateral motor disability due to a pre/perinatal or postnatal event occurring before the 28th day of life. These children's MRIs were classified as malformation, periventricular white matter lesion or cortical-subcortical lesion.[20] Lesions due to a postnatal event occurring after the 28th day of life and before 3 years of age were classified as acquired lesions.[21] A neuropediatrician blind to the clinical assessments inspected all of the images.

Statistical analysis

Descriptive statistics were used to document the children's characteristics, and MM severity. MM-scores were compared between both sides with a Wilcoxon Signed-Rank test. Depending on the type of data, biserial (r_b) or spearman rank (rho) correlations were calculated between MM-scores and general characteristics (age, paretic side), motor impairments, and upper limb activities. In addition, the correlation between MM-scores and the discrepancy of bimanual versus unimanual function was

assessed. This discrepancy was calculated as the ratio of AHA (range 0-100) versus Melbourne-scores (range 0-100). Ratios <1.0 indicate lower AHA compared to Melbourne scores. Correlation coefficients >0.75 were considered good to excellent, 0.50-0.75 moderate to good, 0.25-0.50 fair and <0.25 little or no association.[22] A multiple regression analysis for the Jebsen-Taylor test and the AHA was used to verify if the reported evidence for the univariate relations was maintained when combining the variables MM in test 1 (fist opening and clenching) in each hand and type of lesion. P-values and squared semi-partial correlations (semi r^2) for the three predictors were reported. . Differences in MM between children with different MACS levels or lesion types were analyzed with the Kruskall-Wallis tests and post-hoc Wilcoxon Rank-Sum tests. The level of significance was set at $p<0.05$. Statistical analyses were conducted with SAS Enterprise Guide 4.3 (SAS Institute, Inc., Cary, NC).

Results

Participants

Seventy-eight children (mean age 9y 4m ± 3y 1m; 41 boys; 41 right side paretic) participated in the study. Twenty-one children were classified as MACS level I, 46 as level II, and 11 as level III. Descriptive data of upper limb assessments is provided in Table SII.

Mirror movements

The distribution of MM-scores at each side is provided in Table SIII and Figure 1.

For all three tests, significantly more severe MM were observed in the *non-paretic side* compared to the paretic side ($p\leq0.003$). Over 60% of the children had clear MM (scores ≥2) in the non-paretic side for each test. Of these children, 10% even showed repetitive movements of their non-paretic hand equal to those expected of the moving paretic hand during fist opening/clenching (score 4). Test 1 (fist opening/clenching) also resulted in clear MM in the *paretic side* (score 2, 3) in half of the children. For the other two tests, clear MM in the paretic side were observed in 27% (finger opposition) and 38% (finger tapping) of the children. Significant correlations were found between MM-scores in the paretic and non-paretic side (test 1 *rho*=0.51, test 2 *rho*=0.66, test 3 *rho*=0.60).

Correlation analyses further showed a significant but only fair correlation between MM in the paretic side and age for test 1 (r_b=-0.26), with younger children showing more MM. No significant correlations were found between age and MM in the non-paretic side.

Mirror movements and hand function

For MM in the *non-paretic side*, lower values of grip, forearm and wrist strength in the paretic hand were fairly associated with higher MM-scores for test 1 (range *rho*=-0.38 to -0.32). Similar though lower associations were found for test 3. Muscle tone was not significantly correlated with MM-scores for any test.

Fair correlations were found between all activity measures and MM, whereby children with poorer unimanual capacity and bimanual performance presented with higher MM-scores in the non-paretic side. Highest correlations were found for test 1 (Melbourne Assessment (*rho*=-0.36), Jebsen-Taylor test (*rho*=0.41), AHA (r_b=-0.42)).

MM in the paretic *side* were not correlated with any clinical assessment (Table I).

Figure 2 shows the comparison of MM-scores between the different MACS-levels for test 1. Significantly higher MM-scores were seen in the *non-paretic side* in children with MACS II and III compared to MACS I (p=0.02, Fig. 2.B). Post-hoc comparison showed significant differences in MM-

scores between children with MACS I and II (p=0.01) and a trend between MACS I and III (p=0.05). No significant differences in MM in the *paretic side* were found between the different MACS levels (Fig. 2.A; p>0.3).

Lastly, the correlation between MM-scores and the ratio of bimanual performance versus unimanual capacity was investigated (Table I). Fair correlations between MM-scores and this ratio were found for test 2 in the paretic hand and test 2 and 3 in the non-paretic hand (range r_b=-0.31-0.34). This indicated that children with more MM during finger opposition and finger tapping had a lower performance in bimanual activities compared to their unimanual capacity.

Mirror movements and brain lesions

Five children had a malformation (6%), 43 children showed periventricular lesions (55%), and 22 had cortico-subcortical lesions (28%). Eight children were diagnosed with a postnatally acquired lesion (11%).

MM in the *non-paretic side* were not significantly different between the classification groups (Table II).

A comparison of MM-scores in the *paretic side* showed significant differences between the four groups for fist opening/clenching (p=0.03, Table 2). Visual inspection of the MM-scores showed more MM in children with malformations and periventricular lesions compared to cortico-subcortical and postnatally acquired lesions (Fig. 2, bottom row). Post-hoc comparison confirmed significantly higher MM-scores in children with periventricular lesions versus postnatally acquired lesions (p 0.01).
Figure 3A and 3B show the individual Jebsen-Taylor scores and individual AHA scores respectively of children with bilateral MM (MM-scores of ≥2 for fist opening/clenching), MM only in the paretic hand, MM only in the non-paretic hand and children without MM, for each of the brain lesion types. Overall, children without MM performed better than did children with MM, and best performance was seen in children with periventricular lesions without MM. Remarkably, MM only in the paretic hand occurred exclusively in children with periventricular lesions. Children with MM in both hands showed a large variability in unimanual capacity and bimanual performance, ranging from lacking any ability to grasp and release objects and poor assisted hand use to quite a good unimanual and bimanual function.
Multiple regression analysis for the AHA showed the highest squared semi-partial correlation for type of lesion (*semi* r^2=0.21, p<0.0001), followed by MM in the non-paretic hand (*semi* r^2=0.10, p=0.0008) For the Jebsen-Taylor test, squared semi-partial correlation for type of lesion was 0.23 (p<0.0001), and for MM in the non-paretic hand 0.08 (p=0.0003). MM in the paretic hand showed a non-significant squared semi-partial correlation for the AHA (*semi* r^2=0.07, p=0.56) and for the Jebsen-Taylor test (*semi* r^2=0.04, p=0.99).

Discussion

Moderate to strong MM were present in over 60% of the children. In general, one third showed MM in both hands, another third showed MM only in one hand (mostly the non-paretic) and no MM were seen in the remaining third of the children. This high occurrence of MM compared to the normative data reported by Koerte et al,[4] supports the idea that the MM seen in our group of children with unilateral CP can be considered as abnormal. In line with the literature, we found no or fair associations between age and the occurrence of pathological MM.[1,9] In contrast, physiological MM are known to decrease after 5 years of age and to disappear after 10 years of age.[4] It has been suggested that the suppression of MM with increasing age is related to increasing interhemispheric inhibition through further myelination of the callosal fibers. However, the mechanism underlying physiological MM seems to differ from the mechanisms responsible for MM in CP.[6]

In children with unilateral CP, studies thus far generally point towards significantly more MM in the non-paretic compared to the paretic hand,[1] as confirmed in our study. Although underlying spasticity and muscle weakness might mask the occurrence of MM in the paretic side, the lack of significant correlations between these impairments and MM in the paretic hand does not support this hypothesis. Kuhtz-Buschbeck et al. also noted that asymmetric mirror activity in wrist EMG could not only be explained by a difference in maximum strength.[1] These authors suggested that the higher level of dexterous ability of the non-paretic hand creates a more refined and lateralized pattern of cortical brain activity. Such lateralization would lead to increased interhemispheric inhibition from the non-lesioned towards the lesioned hemisphere, and hence less MM in the paretic hand when moving the non-paretic hand. A third hypothesis would be that MM in the non-paretic hand occur partly to assist paretic hand movements. Symmetrical movements are known to be easier,[23] which might help to overcome the lack of selectivity and strength of the paretic hand. MM in the non-paretic side could thus be considered a nonspecific motor 'overflow' phenomenon in children with significant motor impairments.[13] This idea is further supported by the significant correlations between distal strength deficits, reduced unimanual capacity and the occurrence of MM in the non-paretic hand during paretic hand movements. Also, strong MM in the non-paretic hand were more frequently seen in children with MACS level II and III, i.e. the more severely paretic children, which is in line with the literature.[10,13,24]

MM in the non-paretic hand significantly correlated with bimanual performance, confirming the impact of MM on the performance of bimanual tasks in which differential roles of the two hands are a prerequisite. Correlations were lower than those reported by Kuhtz-Buschbeck et al., though this study lacked a standardized assessment for bimanual function.[1] Interestingly, further exploration of the functional outcomes showed that some children had a poor assistance of the paretic hand in bimanual tasks, despite good unimanual capacity. This discrepancy was significantly correlated with the occurrence of MM in both sides. It thus seems that the symmetric nature of MM disrupts the asymmetric requirements of most bimanual tasks. The occurrence of MM will thereby hinder a fluent and efficient task execution and the child might prefer a unimanual strategy to avoid interference. However, correlations were fair, and other factors such as poor sensory function or developmental disuse, might also play a role.[24]

Brain lesion type might offer an additional explanation for MM. The few available studies have reported more MM in children with early versus late lesions,[13] however, did not differentiate between MM in the paretic and the non-paretic side. Our analysis showed a significant difference in MM of the paretic hand during opening and clenching of the non-paretic hand between children with different lesion types. Children with early lesions (periventricular lesions) had significantly more MM compared to children with lesions that occurred after birth. Brain lesion type has also been related to the structural reorganization of the CST, which is the main motor pathway of the upper limb.[13,25] This reorganization results in ipsilateral control, i.e. the paretic hand is controlled by the non-lesioned hemisphere, or in bilateral control of the paretic hand and is typically seen in children with more extensive lesions in the first, second or early third trimester. In these children, motor function may be maintained through the ipsilateral connections, though at the expense of producing MM.[9] Staudt et al. also noted that MM in the paretic hand only occurred in those children with ipsilateral CST projections, and concluded that only these MM are a sign for the presence of ipsilateral CST reorganization.[26] Holmström et al. confirmed this by reporting strong MM in the paretic hand only in children with ipsilateral motor projections to the paretic hand.[24] However, these authors also showed that apart from lesion type or timing, lesion extent and location also play a role in ipsilateral CST reorganization.[24] Current study results clearly illustrated the complex multifactorial interaction between hand function, the occurrence of MM and lesion type (figure 3), which might account for the generally fair correlations. Whether or not MM are indeed a reliable indicator for ipsilateral motor reorganization and its efficacy remains to be determined in future research combining TMS,

diffusion weighted imaging (DWI) and a quantitative assessment of MM.[12] Also, larger sample sizes of children in the different lesion type groups is needed to boost the statistical power.

This study also warrants some critical reflections. First, scoring of MM was based on a simple, ordinal scale. Although high positive correlations were reported between ordinal ratings and more advanced quantitative measurements,[1] recording of isometric fingertip forces or EMG measures might prove more sensitive. Secondly, we did not include TMS, although it is considered a valuable, non-invasive tool for mapping the motor output to both hands from either cortex. Third, brain lesions were broadly classified. More detailed characterizations of brain lesions are currently possible using quantitative post-processing or semi-quantitative clinical scales,[27] and are likely to provide further insights into the underlying mechanisms of MM in this population.

Still, this is the largest study that systematically assessed MM in children with unilateral CP, based on a representative sample covering the whole range of upper limb functionality and lesion types. We reported more MM in the non-paretic hand compared to the paretic hand, whereby results suggest different factors playing a role in these phenomena. The occurrence of MM in the non-paretic hand when moving the paretic hand seems related to upper limb function. Interestingly, MM seem to interfere with bimanual performance, despite good underlying unimanual capacity. The occurrence of MM in the paretic hand is more related to brain lesion type, whereby children with earlier lesions present with more MM. However, the relationship with brain lesion and type of reorganization, as well as the impact of these factors on treatment response, needs further investigation.

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Table I. Correlations between mirror movements, motor impairments, unimanual capacity and bimanual performance

	Tone[a]		Strength[a]		Grip ratio[b]
	forearm	wrist	forearm	wrist	
Paretic hand					
Fist opening/clenching	0.14	-0.02	-0.10	-0.04	-0.08
Finger opposition	0.22	-0.06	-0.05	0.00	-0.01
Finger tapping	0.15	-0.12	0.01	0.06	-0.01
Non-paretic hand					
Fist opening/clenching	0.15	0.19	***-0.32****	***-0.35****	***-0.38****
Finger opposition	0.06	0.06	-0.12	-0.11	-0.18
Finger tapping	0.14	0.09	-0.22	-0.23	***-0.30****
	Jebsen-Taylor test[a]		**Melb[a]**	**AHA[b]**	**Ratio AHA/Melb[b]**
Paretic hand					
Fist opening/clenching	0.11		-0.02	-0.11	-0.18
Finger opposition	0.01		0.05	-0.10	***-0.31****
Finger tapping	0.00		0.07	-0.03	-0.21
Non-paretic hand					
Fist opening/clenching	***0.41****		***-0.36****	***-0.41****	-0.17
Finger opposition	0.09		-0.08	-0.23	***-0.33****
Finger tapping	0.18		-0.17	***-0.30****	***-0.34****

[a] Spearman rank correlation coefficients; [b] biserial correlation coefficients; Melb: Melbourne Assesssment for Unilateral Upper limb Function; Ratio AHA/Melb: discrepancy between bimanual performance and unimanual capacity scores; *correlation coefficients of 0.25-0.50 indicate a fair relationship

Table II. Mirror movements (median and 25th and 75th centiles) for the different brain lesion types and the concurrent statistical analyses

	Malf N=5	PVL N=43	CSC N=22	Acq N=8	*p* [a]
Paretic hand					
Fist opening/clenching	2 (1-3)	2 (1-3)	1 (0-2)	0 (0-1)	***0.03***
Finger opposition	1.5 (0.5-2)	1 (0-2)	1 (0-1)	0 (0-1)	0.35
Finger tapping	1.5 (0.5-2.5)	1 (1-2)	1 (0-2)	0.5 (0-1)	0.36
Non-paretic hand					
Fist opening/clenching	2 (2-3)	2 (0-3)	2 (2-3)	2 (0-3)	0.64
Finger opposition	1.5 (0.5-2)	2 (1-3)	2 (1-2)	2 (1.5-2)	0.54
Finger tapping	2 (0-3)	2 (1-3)	2 (0-3)	2 (0.5-2)	0.93

Malf: Malformations; PVL: periventricular lesions; CSC: cortico-subcortical lesions; Acq: postnatally acquired lesions; [a] Kruskall-Wallis test

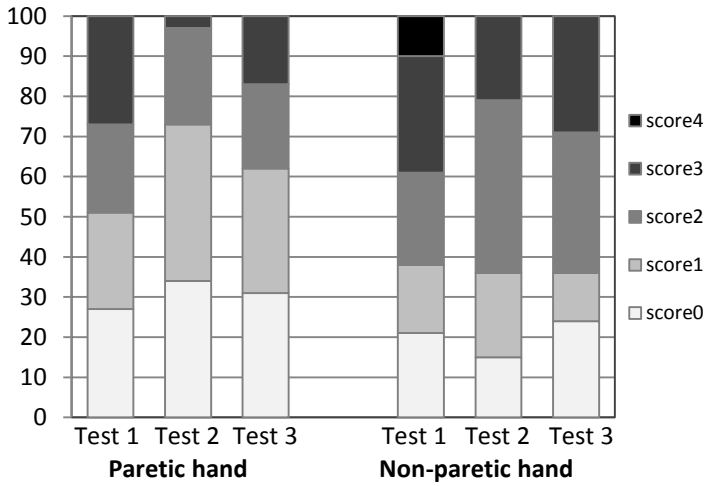

Fig. 1 Distribution of the MM-scores at the paretic and non-paretic hand for the three tests. Test1 = fist opening and clenching; Test2 = finger opposition; Test3 = finger tapping

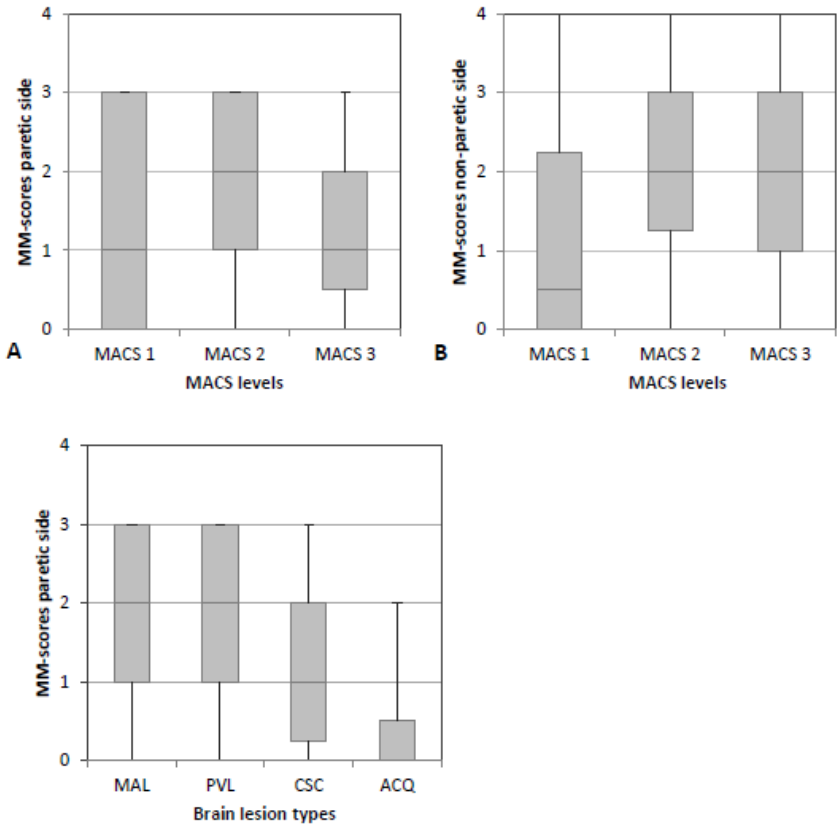

Fig. 2 Median and interquartile ranges of MM-scores for test 1 (fist opening and clenching) for the different MACS levels (top row) at (A) the paretic hand and (B) non-paretic hand and for the different brain lesions (bottom row).

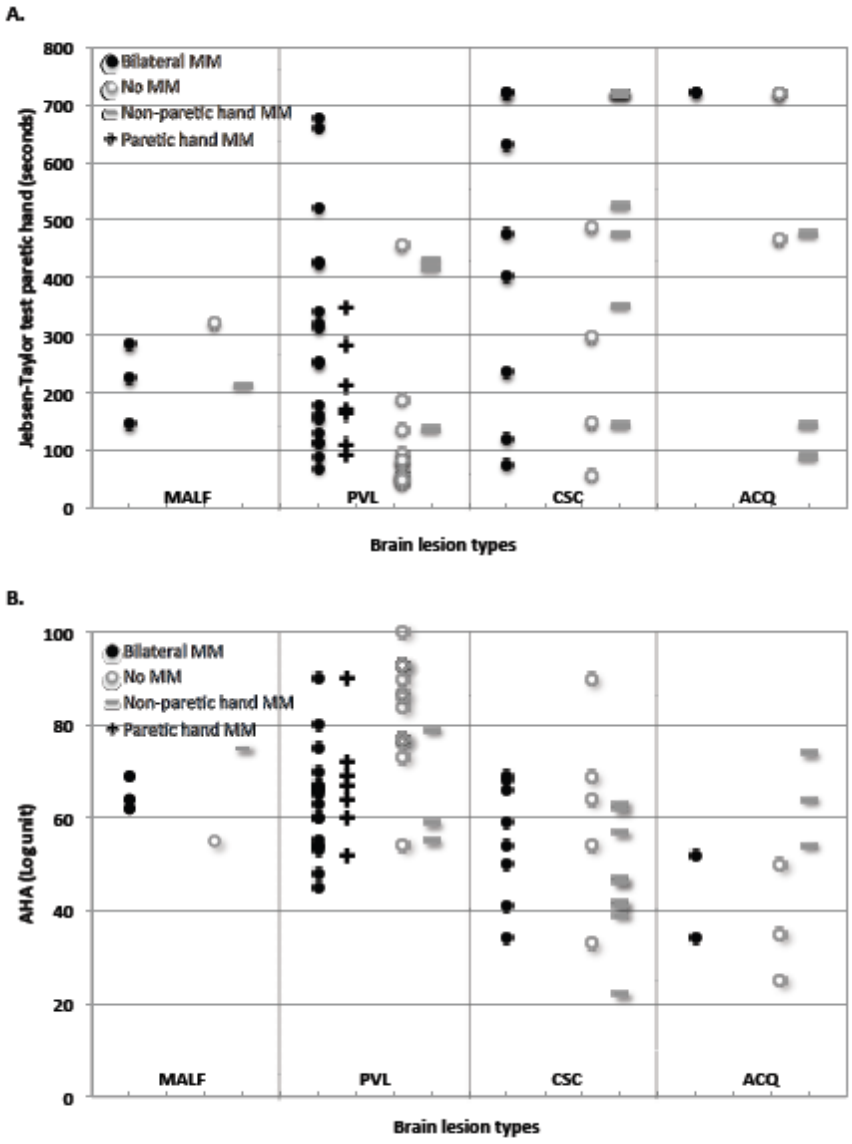

Fig. 3 Individual Jebsen-Taylor (3a; maximum 720 seconds) and AHA scores (3b) of children with bilateral MM (MM-scores of ≥2 on fist opening and clenching), children with MM only in the paretic hand, children without MM and in those with MM in the non-paretic hand only, plotted for every group of brain lesions (MALF= malformations, PVL= periventricular lesions, CSC= cortico-subcortical lesions; ACQ= postnatally acquired lesions).