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▶ **To cite this version:**

Jean-Michel Lemée, Eva Chinier, Pauline Ali, Matthieu Labriffe, Aram ter Minassian, et al.. (Re)organisation of the somatosensory system after early brain lesion: A lateralization index fMRI study. Annals of Physical and Rehabilitation Medicine, Elsevier Masson, 2019, 10.1016/j.rehab.2019.02.001 . hal-02535045

HAL Id: hal-02535045
https://hal.univ-angers.fr/hal-02535045

Submitted on 24 Oct 2022

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Version of Record: https://www.sciencedirect.com/science/article/pii/S1877065719300314
Manuscript_e4d58d53fd8eeaef0dfceb5beaa03b92

(Re)organisation of the somatosensory system after early brain lesion: a lateralization index fMRI study

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Abstract

Objective. To evaluate the relationship between neural (re)organization of the somatosensory cortex and impairment of sensory function (2-point discrimination [2PD]) in individuals with unilateral cerebral palsy.

Methods. We included 21 individuals with unilateral cerebral palsy. 2PD thresholds were evaluated on thumb pads, and activation of the somatosensory cortex was recorded by functional MRI (fMRI) during passive movements of the affected hand. A lateralization index (LI) was calculated for the primary sensory (S1) and secondary sensory (S2) cortices and the correlation between the LI and 2PD thresholds was analysed.

Results. We found a significant negative correlation between the 2PD thresholds and the S2 LI ($r = -0.5$, one-tailed p-value = 0.01) and a trend towards a negative correlation with the S1 LI ($r = -0.4$, one-tailed p-value = 0.05).

Conclusion. High levels of activation in the contralesional hemisphere were associated with high levels of sensory impairment in individuals with unilateral cerebral palsy. The interhemispheric (re)organization of the somatosensory system may not effectively compensate for somatosensory impairment.

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Key Words: cerebral palsy, sensory function, plasticity, functional MRI, lateralization index, brain lesion.

Introduction

Sensory deficits are common in children with unilateral cerebral palsy (UCP) and may contribute to limitations in strength and functional mobility [1]. Standard clinical assessments may underestimate the extent and effect of these deficits on the function of affected individuals. Recent studies have shown that somatosensory processing in patients with UCP requires the structural integrity of the primary sensory (S1) and secondary sensory (S2) areas located in the lesioned postcentral gyrus [2,3]. These findings suggest that the contralesional somatosensory areas do not participate, or only to a small extent, in sensory processing of the affected limbs.

One method to evaluate the functional activation of the somatosensory cortex during sensory tasks is functional MRI (fMRI). fMRI is complementary to behavioural and anatomical measures [4,5] and could provide information regarding the functional (re)organization of the somatosensory cortex after an early brain lesion [6]. A useful paradigm to analyse activation of the somatosensory areas is passive hand movement [7–9]. Passive movement of the affected hand predominantly activates the S1 located in the ipsilesional hemisphere (i.e., contralateral to the stimulated hand) [8] without displacing the functional representation of the sensory system to the healthy (contralesional) hemisphere. Ipsilesional (re)organization of the S1 area appears to be the principal mechanism of compensation after a unilateral early brain lesion [8–10] regardless of the timing of the injury [11]. To date, no studies have evaluated functional (re)organisation in S2.

The lateralization index (LI) is extensively used in fMRI studies to quantify inter-hemispheric activation [12]. It provides an indication of the balance of activation between the 2 brain

hemispheres. LI values are correlated with motor function of the hand [13,14] in patients with stroke, with high contralesional activation of the primary motor area and S1 being associated with high levels of motor impairment [14]. From these results, we could hypothesize that somatosensory function would follow a similar pattern; that is, high activation of the somatosensory areas would be associated with high levels of sensory impairment.

Several fMRI studies have investigated cortical activation during sensory stimulation, but to our knowledge, the relation between the interhemispheric balance of somatosensory activation and sensory impairment in patients with UCP has not been evaluated. Information regarding the functional (re)organisation of the somatosensory system after an early brain lesion and the association with sensory impairment could help in developing optimal rehabilitation strategies.

The primary aim of this study was to analyse the association between neural (re)organisation of the somatosensory cortices (S1 and S2) by using the LI and sensory impairment in individuals with UCP. We hypothesized that 1) the LI would be positive, indicating greater activation of the ipsilesional somatosensory cortex, based on the finding that passive movement of the affected hand in individuals with CP induces activation of the ipsilesional somatosensory brain areas in most cases [8], and 2) the S1 LI would be negatively correlated with the degree of sensory impairment, based on the findings of studies of motor impairment [14]. The secondary aim was to analyse the specific effect of the lesion type (middle cerebral artery [MCA] or periventricular lesions [PVLs]) on the correlations found.

Materials and Methods

Participants

Patients were followed in the paediatric unit of the Physical and Rehabilitation Medicine Department of the University Hospital of Angers. The participants were the same as in Perivier et al. [3]. Inclusion criteria were age between 8 and 20 years with a clinical diagnosis

of cerebral palsy and written consent for participation provided by the legal guardian. Exclusion criteria were contra-indication to MRI or a clinical status likely to cause poor compliance with fMRI acquisition, such as behavioural problems or dystonia. Approval was granted by the local ethics committee (University Hospital in Angers, France). All participants and their parents provided written, informed consent for the research and publication of the results.

Sensory assessment

Two-point discrimination (2PD) thresholds were evaluated bilaterally on the thumb pads by using a 2-point aesthesiometer (Aesthesiometer Lafayette®), as we described previously [3]. Values for this parameter (2PD) have been found to correlate well with many sensory test scores [15]. Two trials were performed for each hand and the mean value was calculated. Higher values reflect more severe impairment.

Imaging procedure

All datasets were acquired on a 1.5 T MR scanner (Magnetom Avanto, Siemens). A T1-weighted anatomical 3D dataset was obtained (176 contiguous sagittal slices, in-plane matrix 256 x 256, yielding a voxel size of 1 x 1 x 1 mm3). A whole-brain echo-planar, EPI sequence (TR = 3000 ms, TE = 50 ms, flip angle = 90°, 32 axial interleaved slice of 5.0-mm slice thickness, in plane matrix = 64 x 64 with a field of view = 240 mm, yielding a voxel size of 3 x 3 x 5 mm^3) was used to acquire a functional series of passive movements of the affected hand.

For the fMRI acquisition, the paradigm was implemented in a block design, with 2 conditions: one passive movement and one resting condition. For both conditions, participants were instructed to look at a fixed red cross positioned in the centre of a black screen. The passive movement condition involved repeated flexion-extension movements of the metacarpophalangeal joints of fingers II-V of the affected hand, performed by an

experimenter (EC) who used her own 2 hands. Passive movement of the affected hand has been found a robust method for evaluating somatosensory cortex activation with fMRI in patients with UCP [7,8,16].

Both conditions were recorded during the same scanning session that involved 112 scans and lasted for 5 min and 36 sec. Each condition was performed for 21 sec and repeated a total of 4 times. The order between the 2 conditions was randomized. E-prime 2.0 software (Psychology Software Tools, Pittbsurgh, PA, USA) was used for the randomization.

Image data processing

Preprocessing was performed by using customised routines as well as functions available in Statistical Parametric Mapping 8 (SPM8; Wellcome Department of Imaging Neuroscience, University College, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Functional images for each participant were preprocessed as described [17,18]. Briefly, functional images were slice time–corrected, realigned, co-registered, spatially normalized and smoothed with an isotropic Gaussian smoothing kernel of 8-mm full-width at half-maximum (FWHM). These preprocessing steps included spatial normalization with a cost-function masking approach [19].

Definition of the somatosensory cortex

The regions of interest (ROIs) used in this study are in Figure 1. These ROIs can be used to calculate LIs for both primary somatosensory cortices (S1) and secondary somatosensory cortices (S2) [20].

Lateralization index (LI) calculation

Individual statistical parametric maps of sensory-related cortical activation were generated for each participant from the passive movement condition data. The difference in activation between the passive movement and the resting conditions was then evaluated with a general linear model approach by using SPM8 software (first-level analysis).

LIs were generated from the raw statistical parametric maps from the first-level analysis. Using a designated SPM-toolbox (LI-toolbox [21]), an overall weighted bootstrapped LI was calculated for each participant from the ROI generated for S1 and S2. The LI indicated differences in the magnitude of activation between the ipsilesional and contralesional S1 and S2 during the passive movement. The LI values range from -1 to +1, where -1 indicates activity only in the contralesional ROIs and +1 activity only in the ipsilesional ROIs. An LI close to 0 (range -0.20 to 0.20) indicates a more bilateral pattern of activation.

Statistical analyses

The associations between the 2PD thresholds and the LI were analysed separately for S1 and S2 by using a Mann-Whitney U test. Because the LI is constrained between -1 and +1, all correlations were assessed by non-parametric Spearman correlation. On the basis of our hypothesis that high activation of the somatosensory areas would be associated with high levels of sensory impairment. We considered negative correlations for S1 and S2 significant if they reached one-tailed $p<0.05$ statistical significance. The specific effect of lesion type (MCA or PVL) on the correlations found was analysed by linear regression of the 2PD thresholds against the S1 and S2 LIs, separately for the MCA and PVL groups.

Results

We included 21 participants (17 males, mean age 13 years and 7 months, range 6 years and 10 months to 20 years and 10 months). Their characteristics are in the Table. Briefly, 12 participants had right UCP (with left-sided brain lesions) and 9 had left UCP (with right-sided brain lesions). Ten had radiological evidence of MCA and 11 PVL. All were born after 35 weeks' gestation.

Characteristics of 2PD

The median value of the 2PD threshold measured on the affected thumb was 2.00 mm (95% confidence interval [CI] [1.00; 3.00]). We found no difference in median threshold between

the MCA and PVL groups (median 2PD 2.00 mm (95% CI [1.00; 7.00]) and 1.00 mm (95% CI [1.00; 3.00]), p=0.26, Mann-Whitney U test). The 2PD thresholds for each participant are in the Table.

Correlation between 2PD and LIs

We found a significant negative correlation between the median 2PD threshold and S2 LI (r = -0.5, 95% CI [-0.77; -0.08], p = 0.01) and a trend towards a negative correlation between the median 2PD threshold and the S1 LI (r = -0.44, 95% CI [-0.69; 0.08], p = 0.05) (Fig. 2).

Stratification of the analysis by lesion type showed these correlations were not significant for the PVL group (S2: r = -0.41, 95% CI [-0.81; 0.25], p= 0.10; S1: r = -0.19, 95% CI [-07; 0.46], p = 0.29). In the MCA group, the negative correlation was significant between the median 2PD threshold and the S2 LI (r = -0.57, 95% CI [-0.89; 0.08], p = 0.04) but not the S1 LI (r = -0.31, 95% CI [-0.79; 0.39], p = 0.19) (Fig. 2).

Discussion

This is one of the first studies to use the LI to analyse the association between the balance of activation in the post-central gyrus and sensory function (2PD). In participants with UCP, passive movement of the affected hand induced greater activation in the ipsilesional cortex, which confirmed our first hypothesis. The results also showed a significant correlation between sensory impairment of the affected hand and S2 LI in these participants and a correlation although not significant with the S1 LI, which confirms our second hypothesis, that high activation of the contralesional hemisphere would be associated with high impairment of sensory function. Therefore, despite signs of inter-hemispheric (re)organization of the somatosensory system, particularly S2, the shift in representation to the contralesional postcentral gyrus did not compensate for the impaired sensory function. Studies of motor impairment in patients with stroke [13,14] and UCP (regardless of type of early brain injury) [22] have also found that a contralateral shift in motor representation does not compensate for

the motor impairment. The results of our study, in agreement with previous studies [2,8,9,20], suggest that (re)organization of the sensory system after an early brain lesion is rare and when it occurs, is ineffective.

Several mechanisms have been proposed to explain inter-hemispheric (re)organisation: altered somatotopic representations of the hand area in S1 in the lesioned hemisphere, altered sensorimotor networks in resting-state fMRI [23], altered white-matter connectivity [24] and displacement of the sensory-motor activation of the lesioned hand to the contralesional hemisphere via axonal sprouting [25]. However, few studies have found evidence of interhemispheric (re)organization of S1. The first report was provided by Maegaki et al. in a patient with unilateral cortical dysplasia [25], followed by Guzzetta et al. [9] and Papadelis et al. [23], who each found evidence of interhemispheric (re)organisation of S1 in only one patient. In our study, we found negative LI values, indicating predominantly contralesional activation, in only 4 of the 21 participants. Moreover, these participants had the most severe sensory impairment (participants 2, 5, 8 and 19; see the Table). In 2 participants (participants 3 and 18), the S1 LI value did not indicate any predominant hemispheric activation. Thus, although inter-hemispheric (re)organisation of S1 after early brain injury is possible, it seems rare and ineffective. This result agrees with functional neuroimaging studies [8–10] and neurophysiological studies [26,27] in this field. fMRI studies have shown that the ipsilesional somatosensory cortices of children with UCP are less responsive to tactile stimulation of the affected body than in healthy children [28,29].

A recent study of children with UCP found different distances in the somatosensory-evoked fields (SEFs) of the ipsilesional hemisphere elicited by tactile stimulation as compared with the contralesional hemisphere, which demonstrates a spatial (re)organization of S1 [23]. This finding could explain the large range of LI values for both S1 and S2 we found. Moreover, in the same previous study, diffusion tensor imaging revealed a decrease in ascending

thalamocortical projections to the lesioned postcentral gyrus, thereby providing further evidence of spatial (re)organisation. The shift in the sensory representation to the contralesional hemisphere shown by the LI in the present study corroborates previous findings that somatosensory processing in the ipsilesional postcentral gyrus is abnormal [23,30].

Activation of the contralesional S2 was predominant relative to the ipsilesional hemisphere in 8 participants (participants 1, 2, 4, 5, 9, 13, 18 and 19). In half of these participants, the (re)organisation of S2 was not associated with a (re)organisation of S1. Two (participants 3 and 10) exhibited more bilateral activation. This observation suggests that interhemispheric (re)organization of S2 occurred more frequently than S1. A study of healthy individuals showed that unilateral peripheral stimulation induced bilateral activation of S2 but not S1 [31]. In individuals with UCP, tactile stimulation or passive movement of the affected hand typically elicits contralesional activation in S2 [32,33]. Contralesional activation in the rolandic operculum after sensory stimulation has also been described in children after hemispherectomy [34].

We cannot determine from the results whether the predominantly contralesional activation of S2 was due to interhemispheric (re)organization of the somatosensory system or bilateral activation of S2, as occurs in healthy individuals during sensory stimulation tasks [31]. Whatever the mechanisms underlying the activation of the contralesional S2, they do not seem sufficient to compensate for the sensory impairment because participants with the greatest contralesional activation had the greatest degree of sensory impairment. The negative correlation we found between the S2 LI and the sensory deficit confirmed the previous hypothesis of the minor role of the non-primary sensory areas of the ipsi- and/or contralesional hemisphere in restoring sensory function [9,32,33]. Thus, although (re)organization of the somatosensory system, demonstrated by activation of the

contralesional sensory cortex, may contribute to sensory function of the hemibody, it is not effective.

After stratifying the analysis by lesion type, the association between the LI and 2PD threshold was no longer significant, especially for the PVL group, although the pattern of the correlations (i.e., negative) did not change, particularly for the MCA group. This finding could be due to the relatively small number of participants who met the strict selection criteria. This choice was deliberate to ensure that the groups were very homogeneous but greatly reduced the statistical power of the analysis. Another explanation could be that the lesion type has a specific influence on the kind of plasticity that occurs in the sensory system. However, clear experimental data are available to show no influence of type of lesion on the type of somatosensory (re)organisation [9]. De Winckel et al. [35] found no major differences in S1 activation between typically developing children and children with UCP and different types of lesions (PVL and cortical lesions). To fully answer this question, further studies with neurophysiological and neuroimaging data are required to provide a greater understanding of neuronal (re)organisation after early brain lesions as well as its effectiveness on sensory function.

Several of the S1 LI values were negative and appeared to be outliers. Whether these outliers highlight the shortcomings of the analysis or represent a real interhemispheric (re)organisation of S1 cannot be answered in this study because of the small sample size and the lack of a sample size calculation. However, even if inter-hemispheric (re)organization occurred in the contralesional S1 of these participants, it did not compensate for the sensory impairment because the 4 participants concerned had the most severely impaired sensory function. Thus, the main results of this study (an apparent ineffectiveness of interhemispheric plasticity of S1 and S2) remain valid. This lack of effective plasticity within the somatosensory system

highlights and indirectly confirms the importance of the structural integrity of the ipsilesional S1 and S2 for preserving somatosensory function after unilateral early brain lesions [3].

A potential limitation of this study is that sensory function was evaluated with only one test. The 2PD test evaluates the somatosensory system as a whole. Threshold values are directly correlated with the density of sensory innervation of the tested area [15], so the results may differ depending on the areas tested; equally, any injury to sensory pathways, such as the medial lemniscal pathway or a peripheral nerve injury [36], will affect the results. The grating orientation task might have also been useful [37], but the 2PD test results have been shown to correlate well with those of many other sensory assessment batteries [15]. Another limitation is that the absence of electrophysiological assessment did not allow for a reliable identification of the somatosensory area and the drawing of further conclusions. Also, this study focused on only S1 and S2 and did not consider other brain regions. However, this choice was deliberate because previous work [8,16,20] suggested that these regions are the major contributors to the restoration of sensory function.

Conclusions

This study found some evidence of a shift of the somatosensory representation to the contralesional hemisphere for both S1 and S2 in individuals with early brain lesions, although shifting of S1 was rarer. In all cases, the shift did not restore sensory function. This work contributes to improving our understanding of neural plasticity within the somatosensory cortical system and suggests that sensory function is optimal when somatosensory activation follows normal physiological networks. These results confirm the importance of the structural integrity of the ipsilesional S1 and S2 for normal somatosensory processing. In addition, the study shows that fMRI and the LI are well suited to the topographical analysis of (re)organisation within the sensory system. These techniques may be useful for evaluating the

effects of therapy on somatosensory plasticity, in particular assessing dynamic changes in inter-hemispheric activation after neurorehabilitation.

Acknowledgements. We wish to thank those who kindly volunteered to participate in the study.

Funding. This research was supported by a grant from the University Hospital of Angers (France), AOI 2011-08, 2011-A0105635 (ANSM), the Société Française de Médecine Physique et Réadaptation (SOFMER) and the Société Francophone d'Etudes et de Recherche sur les Handicaps de l'Enfance (SFERHE). The sponsors of the study had no role in the study design data collection, data analysis, data interpretation, writing of the report, or decision to submit for publication. The authors thank ENJEU[X] (http://enfance-jeunesse.fr/) for their kind help in supporting English editing.

Conflict of interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

FIGURE CAPTIONS

Figure 1. The regions of interest (ROI) used in this study to examine somatosensory brain areas in individuals with unilateral cerebral palsy. The ROIs are superposed on coronal and axial slices by using a gray matter template available in SPM8 software (coronal slice y = -24, axial slices z = 62 and 69). Blue, primary somatosensory cortex; red, secondary somatosensory cortex. See Materials and methods for details.

Figure 2. Correlation between measurement of 2-point discrimination (2PD, y-axis in millimeters) in the affected thumb pad and the lateralization index (LI; x-axis) for secondary somatosensory cortex (S2) on the left panel and primary somatosensory cortex (S1) on the right panel stratified by lesion type. Red diamonds represent participants with a middle

cerebral artery (MCA) stroke, and black diamonds participants with periventricular lesions (PVL).

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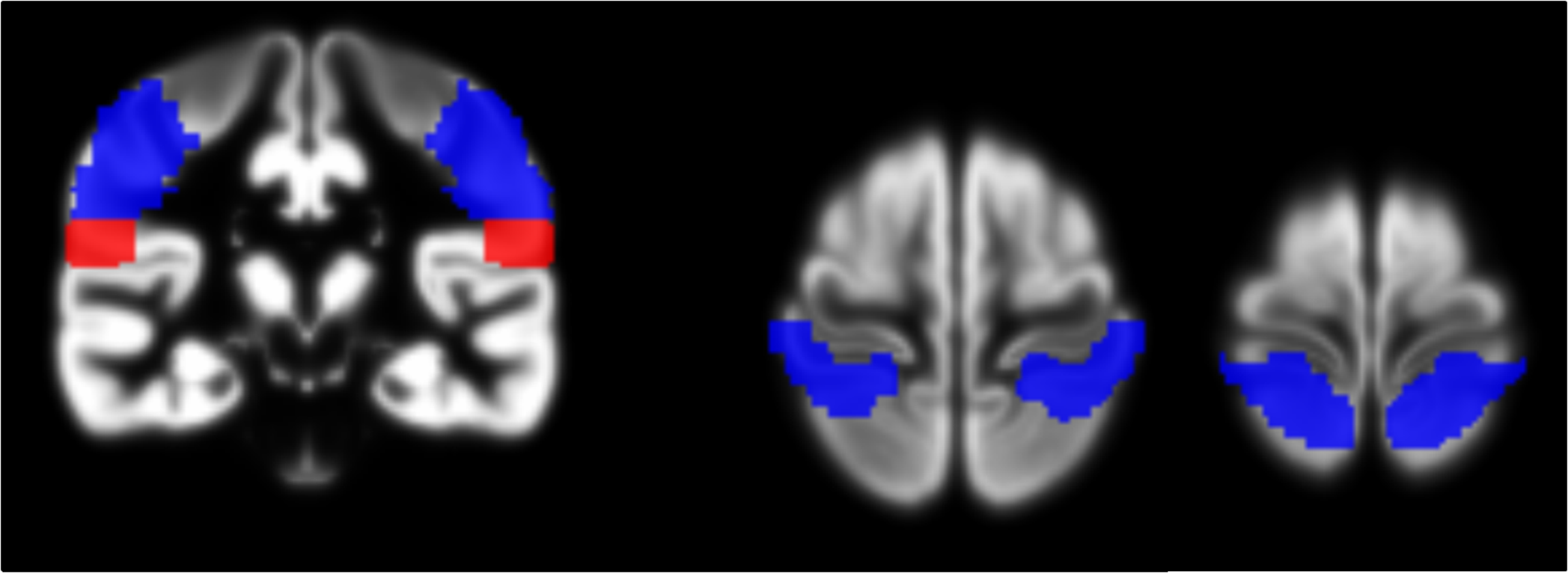

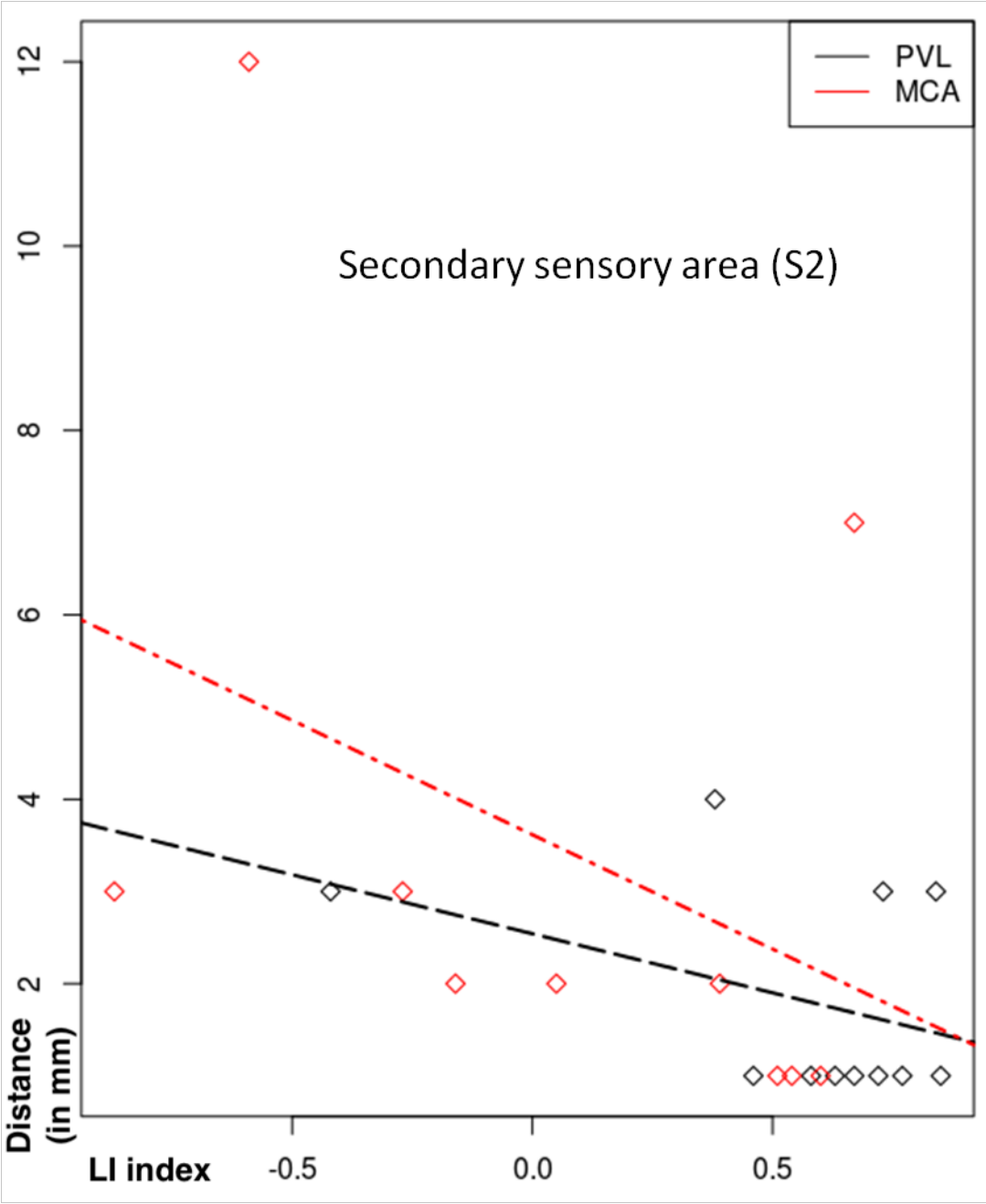
PVL
MCA
Secondary sensory area (S2)
Distance (in mm)
LI index
12
10
8
6
4
2
-0.5
0.0
0.5

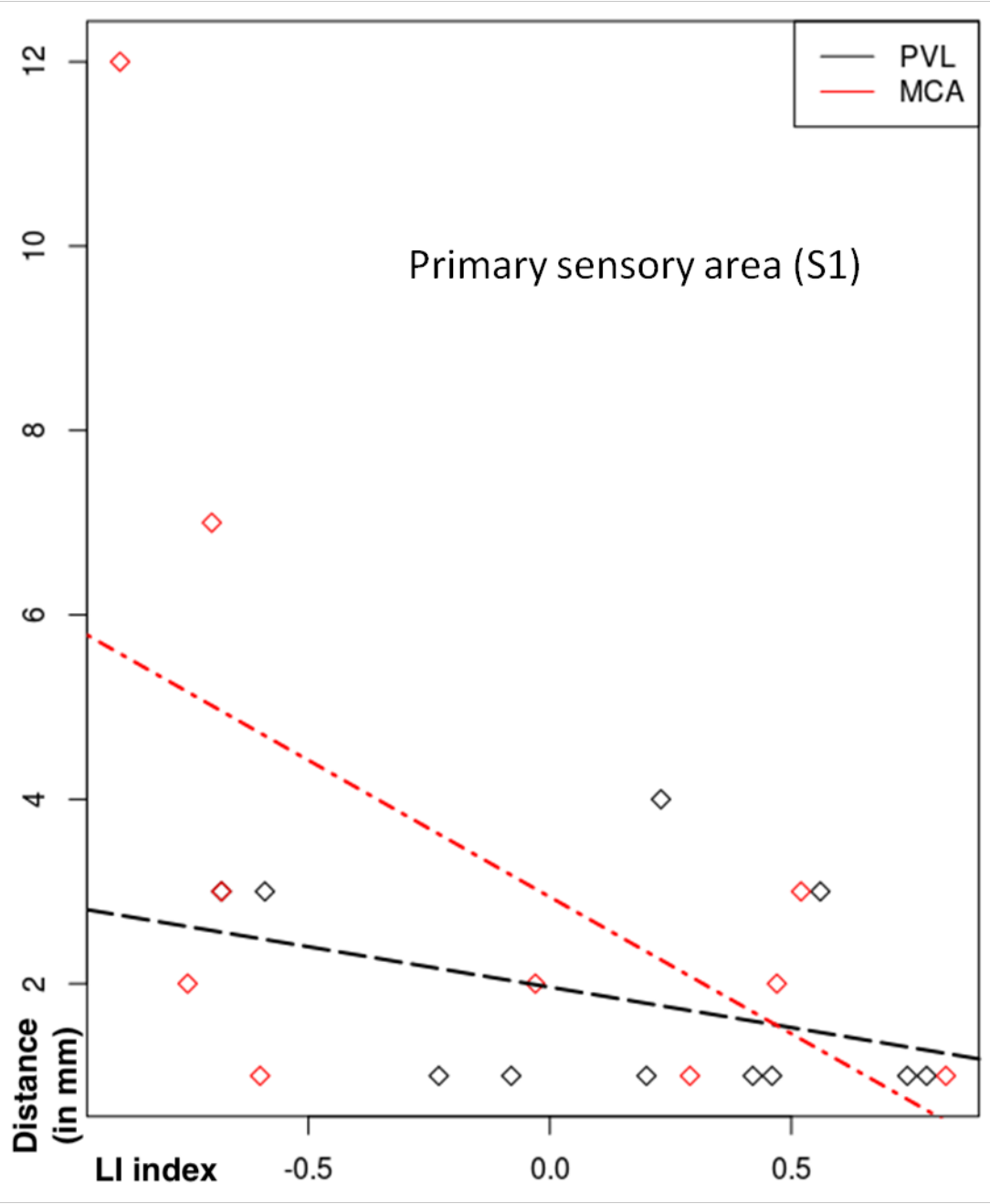
PVL
MCA
Primary sensory area (S1)
Distance (in mm)
LI index
12
10
8
6
4
2
-0.5
0.0
0.5

Table. Demographic data and volumetric values.

yr, years; L/R, left/right; PVL, periventricular lesion; MCA, middle cerebral artery; 2 PD, 2-point discrimination; ph/nph, paretic hand/nonparetic hand; BFMF, bimanual fine motor function test; LI, lateralization index; S1, primary sensory area; S2, secondary sensory area.

Participant	Sex	Age (yr)	Lesion side (L/R)	Lesion type	2PD (mm) (ph/nph)	BFMF	S1 LI	S2 LI
1	M	16	L	PVL	1/1	I	0.46	-0.23
2	F	12	L	MCA	12/2	I	-0.59	-0.89
3	M	10	L	MCA	2/1	II	0.05	-0.03
4	M	9	L	MCA	1/1	I	0.54	-0.6
5	M	13	L	MCA	3/2	III	-0.87	-0.68
6	M	11	L	PVL	1/1	I	0.58	0.42
7	M	12	L	MCA	1/1	I	0.6	0.29
8	M	20	L	MCA	3/2	II	-0.27	0.52
9	M	21	L	MCA	7/3	III	0.67	-0.7
10	M	10	L	PVL	1/1	I	0.63	-0.08
11	M	16	L	PVL	1/1	II	0.77	0.46
12	M	15	R	PVL	1/1	II	0.85	0.78
13	M	11	R	PVL	3/2	I	0.73	-0.68
14	F	18	R	PVL	3/2	II	0.84	0.56
15	F	15	R	PVL	1/1	I	0.67	0.2
16	M	16	R	MCA	1/2	II	0.51	0.82
17	M	6	R	MCA	2/2	I	0.39	0.47
18	F	7	R	MCA	2/2	I	-0.16	-0.75
19	M	13	L	PVL	3/1	II	-0.42	-0.59
20	M	10	R>L	PVL	4/3	I	0.38	0.23
21	M	9	R>L	PVL	1/1	I	0.72	0.74