Bilateral alterations in somatosensory cortical processing in hemiplegic cerebral palsy

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ABBREVIATIONS

MACS	Manual Ability Classification System
MEG	Magnetoencephalography
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex

AIM In individuals with cerebral palsy (CP), cerebral insults during early development may induce profound reorganization of the motor representation. This study determined the extent of alterations in cortical somatosensory functions in adolescents with hemiplegic CP with subcortical brain lesions.

METHOD We recorded somatosensory evoked magnetic fields in response to hand area stimulation from eight adolescents with hemiplegic CP (five females and three males; mean age 14y 6mo, SD 2y 3mo) and eight age- and sex-matched healthy comparison adolescents (mean age 15y 4mo, SD 2y 4mo). All participants in the CP group had purely subcortical brain lesions in magnetic resonance images.

RESULTS The somatosensory representation of the affected limb was contralateral (i.e. ipsilesional), but detailed inspection of the evoked responses showed alterations bilaterally. In the primary somatosensory cortex, the representation areas of digits II and V were in both hemispheres closer to each other in participants with CP than in comparison participants [ANOVA main effect group $F_{1,14}$=5.58; p=0.03]. In addition, the morphology of median nerve evoked fields was altered in the participants with CP.

INTERPRETATION In hemiplegic CP, modification of the somatosensory cortical network extends beyond what would be expected based on the unilateral symptoms and the anatomical lesion. Further understanding of the functional alterations in the sensorimotor networks may aid in developing more precisely designed rehabilitation strategies.

Cerebral palsy (CP), which is caused by an early lesion to the developing brain, is the most common childhood motor disability, affecting 2 to 3 per 1000 liveborn infants in Europe.[1] The symptoms, including difficulties of movement and posture and often also various sensory deficits, severely affect quality of life.

During early development, the human brain has a remarkable capacity to undergo plastic reorganization in response to brain damage. The reorganization in the motor system is bilateral even after unilateral lesions: the contralesional (i.e. ipsilateral to the affected extremity) hemisphere may take over the primary motor control of the palsied hand.[2,3] The reorganization pattern is dependent on the timing, size, and location of the lesion.[2] Larger lesions are more likely to induce ipsilateral reorganization,[3] which, on the other hand, seems the more effective (i.e. better hand function is acquired) the earlier during development the lesion is acquired.[2] As the type of lesion is dependent on age at the time of insult, the functional outcome is worse in individuals with cortico-subcortical lesions as these tend to be large and occur during the late third trimester or perinatally. Ipsilateral or contralateral reorganization may, however, occur with all types of early lesions.[2] In contrast to the motor system, the somatosensory representation remains in the ipsilesional hemisphere,[4,5] as the somatosensory thalamocortical afferents apparently are able to bypass periventricular lesions even in those with contralesionally organized motor representation.[5] These distinct effects of early unilateral insults on motor and somatosensory networks may arise from timing differences in development of major afferent and efferent tracts.[5,6]

Several studies in individuals with CP[7] and in animal models[8] highlight the role of the somatosensory system in shaping motor development and control, but many aspects of this interplay and somatosensory processing in people with CP remain undiscovered. We investigated whether hemiplegic CP, caused by a subcortical brain lesion, is associated with abnormality of

cortical somatosensory functions. We used magnetoencephalography (MEG), which has excellent temporal and sufficient spatial resolution, to detect functional alterations in neural activation patterns in the somatosensory cortices.[9]

What this paper adds

- The somatosensory representation was contralateral (ipsilesional) in the individuals with CP, but there were marked abnormalities in the responses.
- Digit representation at the primary somatosensory cortex was bilaterally altered in participants with hemiplegic CP with subcortical lesions.
- Alterations in somatosensory cortical networks were more widespread than expected in hemiplegic CP.

METHOD

Participants

The participants were eight young people with spastic, hemiplegic CP (five females, three males; mean age 14y 6mo, SD 2y 3mo) and eight age- and sex-matched healthy comparison adolescents (mean age 15y 4mo, SD 2y 4mo). Of those with CP, seven were left- and one right-handed, whereas seven controls were right-handed and one left-handed. A child neurologist (HM) recruited the participants from the Department of Child Neurology at the Helsinki University Central Hospital. The participants were selected based on clinically defined hemiplegia affecting at least the upper extremity and having a subcortical brain lesion in magnetic resonance images (MRIs), and where there was sufficient co-operation for the MEG measurement to be carried out. The comparison group comprised children of the researchers or of their acquaintances. Table I presents details of the clinical background of the participants with CP. All participants gave their informed consent together with their parents. The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the study protocol.

Behavioural tests

An occupational therapist assessed the somatosensory abilities at the tip of digits II and V with Semmes–Weinstein monofilaments (scores 1–6: 6, normal; 4, diminished protective touch; 1, no sensation) and dynamic and static two-point discrimination tests (dynamic: 2–3mm separation, normal; 4–6mm, moderate; 7–9mm, poor, and static: 2–6mm, normal; 7–10mm, moderate; 11–15mm, poor). Motor performance was evaluated with the Manual Ability Classification System (MACS), which ranks the bimanual ability of individuals with CP in everyday life into five levels (I, minor difficulties in handling objects requiring fine motor control; V, severe impairment).[10]

Magnetoencephalography

The tactile stimuli were delivered to the tips of digits II and V of both hands by a thin elastic membrane surrounded by a plastic outer shell. An air puff delivered through a plastic tube (Somatosensory Stimulus Generator, 4-D NeuroImaging, San Diego, CA, USA) expanded the membrane, which then gently tapped on the skin. The digits were stimulated in turns with 1s interstimulus intervals in a single run in the following order: right index, left index, right little, and left little finger. The right and left median nerves were stimulated in separate runs at the wrist with 0.5ms constant-current pulses (intensity just above the motor threshold) and 2s interstimulus intervals.

MEG was recorded in a magnetically shielded room (Euroshield, Finland) with a whole-scalp helmet-shaped sensor array consisting of 306 independent channels: 204 gradiometers and 102 magnetometers (Elekta Neuromag; Elekta Oy, Helsinki, Finland). The sampling rate was 987Hz and bandpass 0.03 to 320Hz. Electro-oculography was recorded from two electrodes, one above the left and the other below the right eye canthus, with a ground on the forehead. An individual Cartesian coordinate system was constructed by digitizing the preauricular points (x-axis: positive to the right) and the nasion (y-axis: perpendicular to the x-axis, positive towards the nasion; z-axis: perpendicular to the x–y plane, positive superiorly). Locations of four position-indicator coils, attached on the scalp, were then determined relative to these anatomical landmarks. In the beginning of each recording set, the coils were fed with excitation current to determine the head position inside the sensor array. During the measurement, the participant sat comfortably watching a self-chosen film without audio.

Artefacts were removed from the raw data before averaging with a spatiotemporal signal space separation method[11] of the MaxFilter software (Elekta Neuromag; Elekta Oy) using the default correlation limit of 0.98 and 4s time window. Thereafter, the averaged (approximately 200 epochs for each stimulation site) tactile stimulation data were digitally low-pass filtered at 90Hz. The median nerve data were not further filtered. Equivalent current dipoles best explaining the source of neural activation were calculated in a spherical head model. In the individuals with CP, the sphere surface was accommodated to the inner skull surface on individual MRIs to determine the origin for the head model. In the comparison group, the origin was set at x=0, y=0, and z=60mm in the head coordinate system, i.e. the sphere was centred 60mm superiorly (along the z-axis) from the origin of the individual coordinate system. This point was chosen based on the mean (0mm, SD 2mm; 2mm, SD 3mm; 62mm, SD 3mm) found for the individuals with CP and previous experience from studies with healthy adults.

After individually determining the channel selection (mean 19 [SD 1.4] channel triplets for primary somatosensory areas), equivalent current dipoles were sequentially calculated with 1ms intervals around the main peaks. The dipole with the greatest moment was selected for statistical analysis. The 300ms analysis period included a 100ms baseline. The following responses were considered. Tactile stimulation: M50[12] from the contralateral primary somatosensory cortex (SI; latency 35–65ms, posterior current dipole orientation) and any activity from the ipsilateral SI. Median nerve stimulation: from contralateral SI N20m (latency 15–25ms, anterior dipole orientation), P35m (30–50ms, posterior dipole orientation), and P60m (50–90ms, posterior dipole orientation), and any clear activity from any other brain area. The mean goodness-of-fit for dipoles from the contralateral SI was 96% (SD 4%) and for those from other areas 89% (SD 5%).

Table I: Background information on the individuals with cerebral palsy

Participant no.	Sex	Age (y)	GA (wk+d)	Epilepsy	Medication	Side of hemiplegia	Lesion type[a]	Lesion size[b]	Lesion location[a]		Lesion extension[a]		2-PD[c]		Monofilament[d]		MACS[e]
									Th	PW	IC	BS	DII	DV	DII	DV	
P1	M	16	31+1	No	–	Left	PVL	3	+	+	–	–	2	2	6	6	III
P2	M	16	42+6	Yes	OXC	Right	Infarction	2	+	+	+	+	np	np	6	6	II
P3	F	11	40+1	No	–	Right	Infarction	2	–	+	+	–	2	2	4	3	I
P4	M	16	28+5	No	–	Right	Porencephaly	1	–	+	–	–	np	np	6	6	II
P5	F	16	34+5	No	–	Right	Infarction	2	–	+	+	+	1	1	6	6	I
P6	F	15	32+2	No	–	Right	Infarction	1	–	+	+	–	1	1	6	6	I
P7	F	12	42+1	No	–	Right	Infarction	1	–	+	+	–	1	1	6	6	I
P8	F	12	41+6	No	–	Right	Infarction	1	–	+	+	–	1	1	6	6	I

[a]The lesion type (arterial infarction or developmental) and location as well as the possible extension along the white matter tracts of the internal capsule and brainstem are also noted: '+' indicates that the lesion involved the area in consideration, whereas '–' indicates that the area was spared of macroscopic lesion in the magnetic resonance images. [b]Lesion size 3 indicates an infarction of the whole middle cerebral artery area or a corresponding size of some other type of lesion; size 1 indicates a spot-type lesion. [c]A 2-PD test score of 1 indicates that both static and dynamic tests for the particular finger were normal and a score of 2 indicates moderate abnormality in one test. For normality limits of 2-point discrimination, see Method. [d]A normal score in the monofilament test is 6, with the worst possible being 1. [e]MACS scores[10] are generally given from I to V, where I signifies minor disability in fine hand motor function. In the CP group, the worst score was III, indicating difficulties in performing everyday activities and dependence on environmental adjustments. CP, cerebral palsy; GA, gestational age; 2-PD, two-point discrimination; MACS, Manual Ability Classification System; Th, thalamus; PW, periventricular white matter; IC, internal capsule; BS, brainstem; DII, digit II; DV, digit V; PVL, periventricular leucomalacia; OXC, oxcarbazepine; np, not performed; M, male; F, female.

Magnetic resonance images

The MRIs were obtained with a 3-tesla unit (Philips Intera Achieva, Amsterdam, the Netherlands). An experienced neuroradiologist (LV) performed the structural analysis from T2-weighted axial and coronal images (slice thickness 3mm) and axial fluid-attenuated inversion recovery (FLAIR) images (4mm). The location and extent of the lesion was scored: 3, infarction of the whole middle cerebral artery area or a corresponding size of some other type of lesion; 1, a spot type lesion; 2, lesions falling in between definitions of score 1 and 3. The lesion type (arterial infarction or developmental), location, and possible extension along the white matter tracts of the internal capsule and brainstem were noted. T1-weighted images were used for MEG-MRI integration and figures.

Statistics

The equivalent current dipole properties were compared with a mixed 2 (group: CP, comparison) ×2 (hemisphere: affected, unaffected) ANOVA, with group being a between-groups factor and hemisphere a within-subjects factor. For tactile data analyses, digit (II,V) was added as another within-subjects factor (mixed 2×2×2 ANOVA). Normality assumption was tested with the Shapiro–Wilk test, sphericity assumption with the Mauchly test, and equality of variances with the Levene test. As the confidence volumes were not normally distributed, they were compared with the Mann–Whitney *U* test. Each individual in the comparison group was assigned to have an 'affected hemisphere' according to the participant's side of lesion to even the number of left or right hemispheres in the statistical comparisons. When an equivalent current dipole could not be modelled, owing to low amplitude or missing activity, the strength was considered zero. Fisher's exact test was used to test the categorical frequencies between participants and the comparison group, such as the existence of certain somatosensory evoked field components. The significance tests were two-tailed unless otherwise stated. The level of statistical significance was set at $p<0.05$.

RESULTS

MRI and behavioural measures

The lesions in the MRIs of all individuals with CP were subcortical. The lesion types, affected areas, and extension of the lesions along the white matter tracts are described in Table I. All had normal or mildly impaired two-point discrimination and monofilament test results. The MACS scores ranged from I to III, corresponding to minor and moderate difficulties in bimanual functions.

Tactile stimulation

Tactile stimulation of digits II and V of both hands evoked the M50 from contralateral SI in all comparison individuals (mean latency of all stimulated fingers: 43ms, SD 4ms) and all participants with CP (45ms, SD 4ms) without significant differences in latency or strength between the groups (Table II). The M50 current sources at the contralateral SI were in somatotopical order: digit V medial and superior to digit II. However, the Euclidian distance between digit II and

Table II: Tactile and median nerve somatosensory evoked magnetic fields from the contralateral primary somatosensory cortex

	Comparison group (*n*=8)		CP group (*n*=8)	
	UH	AH	UH	AH
Tactile				
DII				
Latency (ms)	43 (3)	43 (4)	46 (3)	44 (4)
Q (nAm)	24 (13)	23 (8)	23 (7)	26 (9)
DV				
Latency (ms)	44 (4)	43 (5)	46 (5)	44 (4)
Q (nAm)	18 (7)	22 (9)	16 (8)	22 (8)
Median nerve				
N20m				
n	8	8	8	5
Latency (ms)	21 (1)	20 (1)	20 (1)	20 (1)
Q (nAm)	18 (9)	22 (8)	19 (11)	26 (16)
P25m				
n	1	2	6	8
Latency (ms)	28	26 (2)	25 (2)	25 (1)
Q (nAm)	41	22 (16)	43 (28)	45 (28)
P35m				
n	8	8	8	8
Latency (ms)	33 (2)	34 (3)	37 (5)[a]	39 (4)[a]
Q (nAm)	54 (10)	64 (23)	49 (18)	50 (16)
P60m				
n	8	8	8	6
Latency (ms)	66 (8)	68 (6)	62 (4)	66 (11)
Q (nAm)	64 (23)	54 (10)	49 (23)	32 (25)[a]

Mean (SD) of response latencies and source strengths for the tactile M50 response and various median nerve responses; for the latter, the number of individuals (*n*) displaying each response is also indicated. P35m was delayed in both hemispheres of individuals with CP, and P60m strength was weaker in their affected hemisphere. [a]Values significantly different from controls. UH, unaffected hemisphere; AH, affected hemisphere; DII, digit II; Q, source strength; DV, digit V.

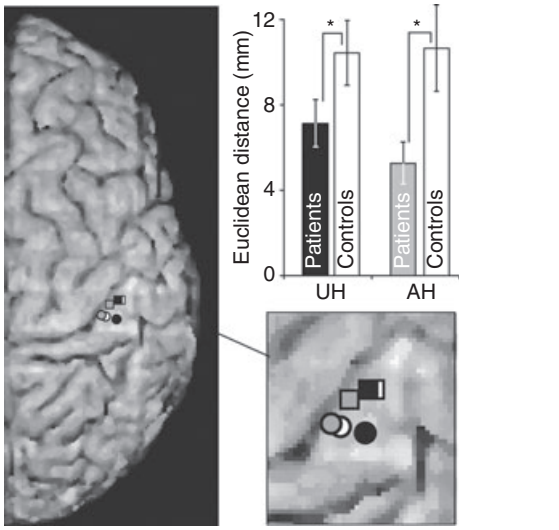

Figure 1: A schematic illustration showing the Euclidean distances separating digit II and V representation areas in adolescents with cerebral palsy (CP) and members of a comparison group. The group average (from the eight individuals with CP and eight comparison individuals) locations of M50 current dipole to stimulation of digit II (circles) and V (squares) in participants' affected (grey) and unaffected hemisphere (black) and one hemisphere ('affected', white [each member of the comparison group was assigned to have an 'affected hemisphere' according to the participant's side of lesion, see Method]) of controls are displayed on an average brain. For comparison, all locations are superimposed on the same hemisphere. Note the smaller distance between the dipole locations of the two fingers in the individuals with CP, particularly the affected hemisphere. The graph shows the average Euclidean distances with the narrow bars indicating standard errors of the mean. *$p \leq 0.05$ in one-tailed independent samples *t*-test. UH, unaffected hemisphere; AH, affected hemisphere.

V locations was significantly shorter in the CP group than in the comparison group in both the affected hemisphere (CP group: 5.3mm, SD 2.8mm; comparison group: mean 10.6mm, SD 5.8mm) and the unaffected hemisphere (CP group: mean 7.1mm, SD 3.2mm; comparison group: mean 10.5mm, SD 4.4mm). This was reflected in the main effect of group in ANOVA [$F_{1,14}$=5.58; p=0.03,η_p^2=0.29]. However, the main effect of hemisphere and the hemisphere × group interaction were not significant, indicating that the group difference was of similar magnitude in the affected and unaffected hemispheres (Fig. 1). There were no differences between the CP and comparison groups in goodness-of-fit or confidence volume of the fits. The ipsilateral SI was activated more frequently in the participants with CP (seven out of eight participants, seven digits of the normal hand, latency 66ms [SD 27ms]; four digits of the palsied hand, 55ms [SD 5ms]) than in comparison adolescents (one out of eight individuals, three digits, 58ms [SD 3ms]) (Fisher's exact test, p=0.01).

Median nerve stimulation

In all individuals in the comparison group, stimulation of both median nerves elicited the three early responses from the contralateral SI: N20m, P35m, and P60m (Table II). An additional peak at around 25ms (P25m) preceded the P35m in two comparison individuals (in one bilaterally and one unilaterally). Similar to the P35m, the P25m was generated by a posteriorly pointing dipolar source. In the comparison group, the contralateral secondary somatosensory cortex (SII) was activated after stimulation of 11 out of 16 median nerves and the ipsilateral SII after stimulation of 12 out of 16 median nerves. No activity from the ipsilateral SI within 100ms was detected in any control after median nerve stimulation.

N20m, P35m, and P60m were also present in the unaffected hemisphere of all participants with CP. In the affected hemisphere, N20m was absent in three and P60m in two individuals (Fig. 2). P25m was present in six out of eight unaffected and eight out of eight affected hemispheres, that is, significantly more often than in the comparison group (two individuals, three out of 16 hemispheres; Fisher's exact test, p=0.007). The P35m peaked, on average, 4.5ms later in the participants with CP than in comparison individuals, as reflected by the main effect of group in ANOVA [$F_{1,14}$=7.11; p=0.02,η_p^2=0.34]. Again, neither the main effect of hemisphere nor the hemisphere×group interaction was significant. The N20m and P35m dipoles were located at SI in the MRIs of seven participants with CP; in one the P35m dipole was slightly anterior to

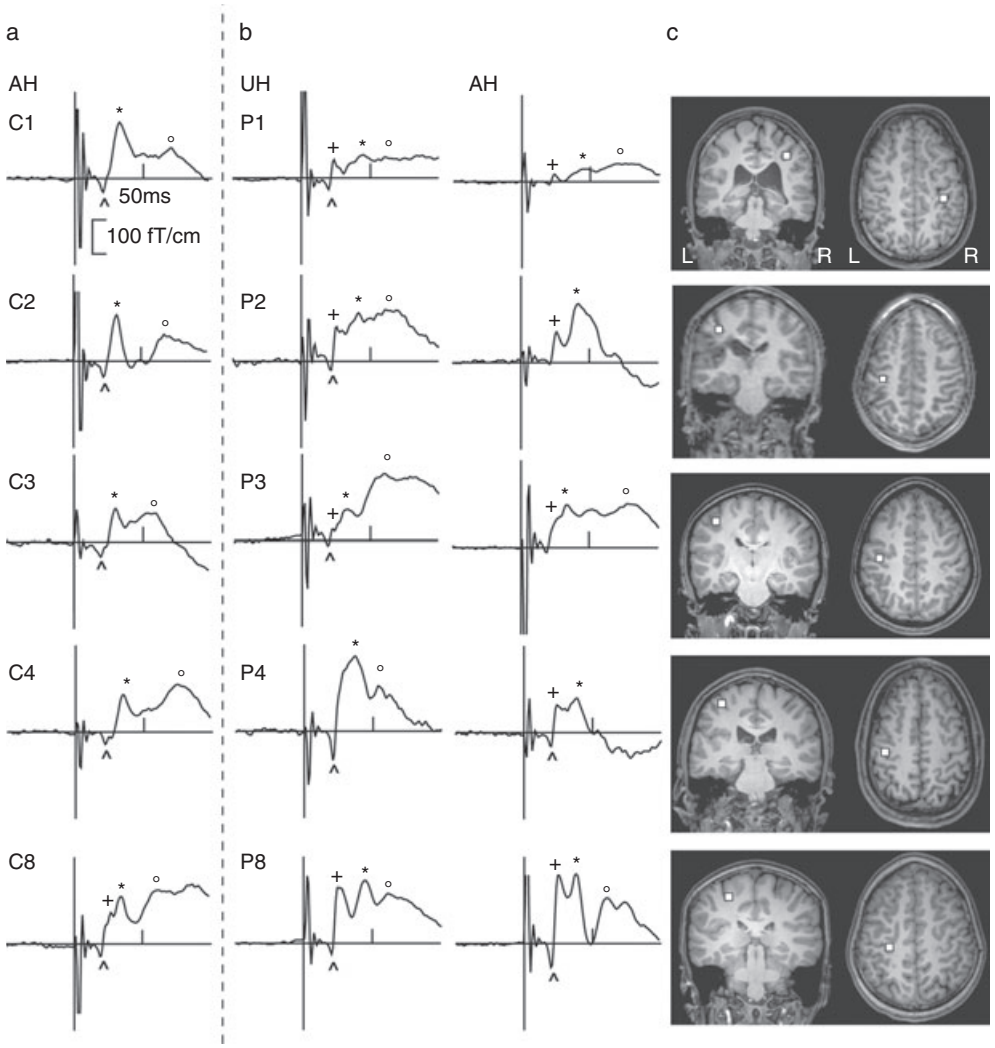

Figure 2: Somatosensory evoked magnetic fields from the contralateral SI in response to median nerve stimulation. Waveforms from one gradiometer channel with maximal signal showing the median nerve responses from contralateral SI in (a) five comparison individuals (C1–C4 and C8) and (b) five individuals with CP (P1–P4 with one or two of the three main components missing, P8 with normal responses i.e. with N20m, P35m, and P60m present). The waveforms are shown to stimulation of both hands in individuals with CP and one hand of comparison adolescents to enable comparison within and between individuals. The N20m is marked with `^', P25m with `+', P35m with `*', and P60m with `○'. Note that the P25m is present in all individuals with CP but in only one member of the comparison group. (c) The P35m to stimulation of the palsied hand was detectable at the affected hemisphere of all affected individuals and it is superimposed on the individual magnetic resonance images. SI, primary somatosensory cortex; CP, cerebral palsy; AH, affected hemisphere; UH, unaffected hemisphere; L, left; R, right.

the central sulcus (N20m was absent in this individual). SII responses were detected at a similar incidence in the CP and comparison groups. Owing to the great variability in latencies and strength, no further statistical comparisons of the SII responses were performed. Median nerve stimulation did not evoke activity in the ipsilateral SI within the first 100ms in any participant.

DISCUSSION

We used a modern neurophysiological method, MEG, to demonstrate alterations in somatosensory processing in individuals with hemiplegic CP. Although the participants' clinical symptoms were unilateral, the alterations in cortical somatosensory processing were bilateral. In both hemispheres, the cortical representation areas for digits II and V at the contralateral SI were located closer to each other in the participants with CP than in the comparison group. Also, the morphology of the median nerve evoked responses was bilaterally altered. In addition, activity at the ipsilateral SI (mostly after stimulation of the unaffected hand) was more frequently seen in the CP group than in the comparison group.

The shorter distance between digit II and V representation areas in the individuals with CP may either be directly caused by the lesion or reflect inappropriate sensory experience during development. In owl monkeys, surgical fusion of adjacent digits results in a fusion of contralateral SI receptive fields,[13] as does

training consisting of synchronous tactile stimulation to adjacent fingers.[14] In two humans with syndactyly, initially fused cortical finger representations were distanced from each other after surgical separation of the congenitally fused fingers.[15] Altered peripheral input in conditions including amputations[16] and carpal tunnel syndrome[17] also induces contralateral SI plasticity. Our findings in adolescents with CP could reflect a fusion of the cortical finger representation areas caused by inappropriate sensory experience during development, for example due to difficulties in fine hand motor control. The unchanged source strength also supports such a fusion over simple shrinking of contralateral SI representation areas or, in other words, a smaller number of activated neurons.

Also, the median nerve responses in both hemispheres were morphologically different between the two groups. In the individuals with CP, an additional peak, P25m, preceded the P35m, which was slightly delayed compared with the comparison group. In healthy adults, the P25m may appear as a notch in the ascending phase of P35m, rather than as a prominent peak, but becomes more pronounced with higher stimulation frequencies (interstimulus interval 300ms; our own unpublished observation). In our participants, the prominent P25m together with the delayed P35m may reflect dysfunction in the information processing at the contralateral SI or interplay between SI and the primary motor cortex. (See Huttunen[18] for a discussion concerning the neural origin of the P35m.) However, the exact generation mechanisms and behavioural significance of these responses following the initial N20m remain unknown at present.

In individuals with CP, the interplay between the primary somatosensory cortices of the affected and unaffected hemisphere may also be altered, as the above-mentioned changes in the somatosensory evoked magnetic fields were bilateral. Although we cannot exclude minor defects in the afferent pathway or cortex also on the unaffected side, modifications in callosal connections may also induce functional changes in the unaffected hemisphere.[19] Bilateral alterations in finger representations at SI have previously been described in humans with unilateral focal hand dystonia[20] as well as in an animal model of the same condition.[21] Furthermore, in macaques and flying foxes, an induced cortical, unilateral lesion of SI temporarily increased receptive field size of the homologous body part in the opposite SI.[22]

Ipsilateral SI responses were detected more often in the CP group than in the comparison group. In healthy adults, ipsilateral SI activation has only rarely been reported in response to hand area stimulation.[23] It should be noted, however, that our results generally support the earlier results of normal contralateral representation of somatosensory functions as most of these ipsilateral responses in our participants were evoked by stimulation of the normal hand and had longer latencies than the contralateral responses. Ipsilateral SI responses have been reported to be enhanced in Unverricht–Lundborg-type progressive myoclonus epilepsy[24] and in an individual with complex regional pain syndrome.[25] The presence of ipsilateral SI responses may reflect reduced inhibition of commissural fibres.[25] Thus, in our participants too, the frequent ipsilateral SI responses in the affected hemisphere, evoked by stimulation of the healthy hand, may reflect alterations in the interplay between the hemispheres mediated by callosal fibres.

Even though our study is limited by the relatively small number of participants, we found significant differences between those CP and the comparison individuals. The variance of our participants' clinical backgrounds reflects the situation in clinical practice. The number of participants did not allow statistical inferences to be drawn about the effects of lesion type (infarction/developmental) or preterm birth. However, there were no obvious qualitative differences in the somatosensory evoked magnetic fields. The participants missing some median nerve response components tended to have larger lesions in MRI and worse scores in the behavioural tests, but statistical correlations of these measures were beyond our scope. We also did not include individuals with lesions affecting the cortex who may have worse outcome owing to less effective reorganization of, at least, the motor system.[2] Previously, normal contralateral somatosensory responses have been demonstrated in individuals with CP with cortico-subcortical defects,[4] but more detailed analysis of the sources has not been reported. Thus, in the future it will be interesting to correlate the changes in the somatosensory responses quantitatively with behavioural and neuroimaging data in a larger number of individuals, including those with cortico-subcortical lesions. Finally, in our study group, there was a discrepancy in handedness between the groups. However, this should not have confounded the results as in the comparison group no differences in somatosensory responses existed between the dominant and non-dominant hand or between the hemispheres.

The bilateral alterations of somatosensory processing in individuals with hemiplegic CP with subcortical brain lesions highlight the complexity of functional reorganization after an early brain insult. Further understanding of the functions of the sensorimotor networks in CP may aid in developing more precisely designed rehabilitation and treatment strategies, such as individually targeted transcranial magnetic stimulation.

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