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Original article

Brain activation changes following motor training in children with unilateral cerebral palsy: An fMRI study

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ABSTRACT

Background: Intensive motor-learning-based interventions have demonstrated efficacy for improving motor function in children with unilateral spastic cerebral palsy (USCP). Although this improvement has been associated mainly with neuroplastic changes in the primary sensori-motor cortices, this plasticity may also involve a wider fronto-parietal network for motor learning.
Objective: To determine whether hand-arm bimanual intensive therapy including lower extremities (HABIT-ILE) induces brain activation changes in an extensive network for motor skill learning and whether these changes are related to functional changes observed after HABIT-ILE.
Methods: In total, 25 children with USCP were behaviourally assessed in manual dexterity and everyday activities before and after HABIT-ILE. Functional imagery monitored brain activity while participants manipulated objects using their less-affected, more-affected or both hands. Two random-effects-group analyses performed at the whole-brain level assessed the brain activity network before and after therapy. Three other random-effects-group analyses assessed brain activity changes after therapy. Spearman's correlations were used to evaluate the correlation between behavioural and brain activity changes.
Results: The same fronto-parietal network was identified before and after therapy. After the intervention, the more-affected hand manipulation elicited a decrease in activity on the motor cortex of the non-lesional hemisphere and an increase in activity on motor areas of the lesional hemisphere. The less-affected hand manipulation generated a decrease in activity of sensorimotor areas in the non-lesional hemisphere. Both-hands manipulation elicited an increase in activity of both hemispheres. Furthermore, we observed an association between brain activity changes and changes in everyday activity assessments.
Conclusion: Brain activation changes were observed in a fronto-parietal network underlying motor skill learning with HABIT-ILE in children with USCP. Two different patterns were observed, probably related to different phases of motor skill learning, representing an increased practice-dependent brain recruitment or a brain activation refinement by more efficient means.
ClinicalTrials.gov: NCT01700777 & NCT02667613.

1. Introduction

Cerebral palsy (CP) occurs in 2 to 3.6 of 1000 children [1], being the consequence of brain structural abnormalities, including periventricular leukomalacia, brain malformations and intracranial hemorrhage [1]. These lesions usually induce motor deficits having a strong impact at the activity level and autonomy in the person with CP; therefore, much attention has been dedicated to develop efficacious motor interventions [2].

Over the last 15 years, intensive rehabilitation interventions have been successfully developed for improving upper-extremity function in children with unilateral spastic cerebral palsy (USCP [2]). These interventions, including constraint-induced movement therapy (CIMT [3]), hand-arm bimanual intensive therapy [4] or hand-arm bimanual intensive therapy including lower extremities

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(HABIT-ILE) [5], are based on motor-skill learning principles. They include the use of shaping, positive reinforcement and high intensity with repetitive practice, whereby the skill performance improves faster at the beginning and reaches asymptotic levels toward the end [6]. These principles induce the acquisition of new motor skills and, as demonstrated in animal and healthy human models, should produce neuroplastic changes, such as reorganisation of the extremities' cortical representation and synaptogenesis in the motor cortex [7,8].

In human research, although some changes were observed in motor brain areas, specifically evaluated with transcranial magnetic stimulation [9], insights from neuroimaging allow for identifying a neural network involved in motor skill learning. This system involves an extensive fronto-parietal network, including the primary motor cortex, supplementary motor area, premotor cortex, primary sensory cortex, prefrontal cortex, anterior cingulate cortex and posterior parietal cortex, as well as subcortical structures such as the cerebellum and basal ganglia [10,11]. Moreover, in healthy individuals, two phases of motor-skill learning have been associated with different brain activation patterns: an early phase leading to increased brain activation and a later phase in which the task is more automatic and the brain activation is decreased [12].

In children with CP, a few studies have investigated the neuroplastic changes related to intensive motor training interventions. Studies of CIMT focused on primary motor and sensory cortex reported increased activation of the primary motor cortex contralateral to the more-affected hand after the intervention [13]. In addition, some studies reported a decrease in activation of the non-affected sensori-motor cortex [14]. These studies were based on case series of few children and on activation resulting from global movements (no manipulative tasks), performed solely with each hand separately [13]. Some of these studies suggested that an increase or decrease in activation may depend on the corticospinal organisation of the children (contralateral, ipsilateral or bilateral) [14,15].

The aim of the present study was to investigate the activation changes in a larger group of children with USCP after HABIT-ILE, focusing on the complete cortical network for motor skill learning, with a task requiring manipulative skills, performed with each hand separately or both combined. We hypothesised that the brain activity changes could be related to the phases of motor skill learning, mainly reflected in the activity of sensorimotor cortex, this last activity probably related to the behavioural improvement observed after therapy.

The reporting of this paper follows the guidelines of the Organisation for human brain mapping committee on best practices in data analysis and sharing (COBIDAS) in neuroimaging by using MRI [16].

2. Material and methods

2.1. Participants

For this before–after non-controlled study, we included 29 children (15 girls, mean [SD] age 8.5 [2.2] years) with a diagnosis of USCP (18 right hemiparesis). The USCP was classified by the Manual Ability Classification System [17] as levels I (n = 4) or II (n = 25) and by the Gross Motor Function Classification System [18] as levels I (n = 15) or II (n = 14). Brain lesions were classified as cortical malformation (n = 4), periventricular injury (n = 10) or a cortical/subcortical lesion (n = 15) by using the criteria proposed by Krägeloh–Mann and Horber [19]. All parents/legal guardians and children provided their written informed consent. This study was approved by the ethical committee of the Université catholique de Louvain. Data were collected in the context of 2 clinical trials (ClinicalTrials.gov: NCT01700777 and NCT02667613).

Children were recruited from centres dedicated to treating CP in Belgium to participate in a 2-week HABIT-ILE intervention performed in Brussels, Belgium, during the summers of 2013, 2014 and 2015 (see Appendix). Inclusion criteria were:

- age 6 to 16 years;
- school level equal to typically developing peers;
- ability to follow instructions and complete testing;
- diagnosis of a unilateral spastic form of CP.

Exclusion criteria were:

- uncontrolled seizures;
- botulinum toxin injections or orthopedic surgery within the previous 12 months or planned within the study period;
- visual problems likely to interfere with treatment/testing.

The behavioural outcomes of some children included in this study were previously published [20].

2.2. Intensive training

Children participated in a HABIT-ILE treatment for 9 hr/day during 10 consecutive weekdays (90 hours total). The specificity of the content and the rationale behind HABIT-ILE were published in the original methodological paper [21]. HABIT-ILE uses structured bimanual tasks requiring simultaneous control and coordination of movements of the upper and lower extremities, as well as functional tasks requiring bimanual use and the stimulation of lower extremities [5,21]. The motor tasks are graded and gradually progress in difficulty. HABIT-ILE takes into consideration functional goals expressed by children and their parents and is designed to be child-friendly, with one interventionist for each child. From impairments identified by the assessments before HABIT-ILE, supervisors selected activities and tasks individualised for each child that evolved progressively toward more challenging activities.

2.3. Behavioural assessments

The more-affected (MA) and less-affected (LA) hand of each child was assessed the week before (s1) and the week after (s2) the HABIT-ILE. Dexterity was measured with the Box and Block test (BBT [22]); stereognosis was assessed with the Manual Form Perception Test [23]. Manual ability in daily life activities was measured with the ABILHAND-kids questionnaire [24], and performance of the MA hand in bimanual activities was measured with the Assisting Hand Assessment (AHA [25]).

2.4. Functional MRI (fMRI) procedure

Two MRI assessments were performed at the same times as behavioural assessments (s1 and s2). Preparation for fMRI consisted of presenting an information session to parents/children, with an instructional video and a simulation of the task performed in the scanner 30 min before the verum examination. One parent/caregiver remained in the scanning room during the entire session to assure the child.

During the fMRI examination, children were provided 6×3 auditory commands ("left hand", "right hand", "both hands") per sequence via headset. The task was performed without visual feedback, using a circular or a triangular object (both measuring 1.5 cm), with only the left or right hand, or by griping the object

simultaneously with both hands regarding the command. After the command, children performed the task requested: opened the hand (or hands in the "both hands" condition) to receive and grasp the object(s); closed the hand(s) and manipulated the object(s), moving it inside the hand(s) to recognise it. When the command "rest" was heard, children released the object(s) by opening their hand(s) so the object(s) was taken by an experienced examiner, who remained inside the scanning room during the entire fMRI session, to present/remove the objects and monitor hand movements. A block design paradigm was used, with experimental blocks (duration: 11.25 secs) alternating with resting periods (9 secs) in 3 sequences of 373.5 secs each. At each MRI session, 3 runs were performed. In each run, the task was performed in random sequence 6 times with the right hand (RC), 6 with the left hand (LC) and 6 with both hands (BC).

2.5. 3D-MRI and fMRI acquisition

Structural brain imaging was obtained on a 3 Tesla MRI unit (Achieva, Philips Healthcare, Best, The Netherlands) with a 32-channel phased-array head coil, using a 3-D fast T1-weighted gradient echo sequence with an inversion pre-pulse: Turbo field echo, repetition time (TR) = 9.1 ms, echo time (TE) = 4.6 ms, flip angle = 8°, 150 slices, 1-mm thickness, in-plane resolution = 0.81 × 0.95 mm^2 (acquisition) reconstructed in 0.705 × 0.705 mm^2. The field of view was 220 × 197 mm^2, acquisition matrix = 296 × 247 (reconstruction 320^2) and the SENSE factor (parallel imaging) was 1.5.

Blood oxygen level-dependent fMRI data were acquired by using a 2-D single-shot T2*-weighted gradient echo-planar imaging sequence (TR = 2250 ms, TE = 32 ms) with 38 axial slices (thickness = 3 mm) acquired in ascending interleave sequence. The field of view was 220 mm^2. The in-plane resolution was 1.964 × 1.964 mm^2.

2.6. fMRI pre-processing

All MRI data analysis involved using BrainVoyager 20.6 (Brain Innovatio, Maastricht, The Netherlands) with standard preprocessing procedures. fMRI data preprocessing included slice scan time correction, head motion correction and high-pass filtering (cut-off frequency: 0.005 Hz) in the frequency domain. Imaging data were mirrored horizontally for children with lesions in the right hemicortex. The resulting matching brain images were registered to the standardised Talairach space and re-sliced to a final voxel size of 3 × 3 × 3 mm. Single-subject functional data were then spatially smoothed (5 mm full width at half maximum) to reduce inter-subject anatomical variability. Functional data were further analysed with a multiple regression model (general linear model) considering 3 experimental conditions (RC, LC, BC). In this model, the beta weights quantified the potential contribution of each predictor in each voxel time course. The predictor time courses of the regression model were computed based on a linear model of the presumed relation between neural activity and hemodynamic response, assuming a rectangular neural response convolved with a standard hemodynamic response function (two-gamma hemodynamic response function) during phases of active conditions.

2.7. Data analysis

2.7.1. Behavioural data

The mean score of each behavioural test (BBT, stereognosis test, ABILHAND-kids and AHA) was compared before and after HABIT-ILE by paired *t*-test.

2.7.2. fMRI data

Two random-effects group analyses [26] were first performed at the whole-brain level with the following contrasts: [(RCs1 + LCs1 + BCs1) > rest] (s1: session before HABIT-ILE), [(RCs2 + LCs2 + BCs2) > rest] (s2: session after HABIT-ILE) with false discovery rate procedure $P < 0.01$ combined with a cluster size threshold adjustment (minimum cluster size: 184 functional voxels) to achieve a corrected $P < 0.05$. This procedure was based on the Forman et al. [27] Monte-Carlo simulation approach, extended to 3-D datasets with the BrainVoyager 20.6 threshold size plug-in. In addition, a conjunction analysis was performed to determine common areas between the before and after HABIT-ILE conditions.

Secondly, 3 random-effects group analyses [26] were performed to identify possible changes in the brain activation after HABIT-ILE. The difference before and after therapy in 3 conditions was calculated: more-affected hand [(RCs2 > rest) minus (RCs1 > rest)], less-affected hand [(LCs2 > rest) minus (LCs1 > rest)] and both hands [(BCs2 > rest) minus (BCs1 > rest)], rest)], at a false discovery rate procedure $P < 0.05$ combined with a cluster size threshold adjustment (minimum cluster size: 184 functional voxels) to achieve a corrected $P < 0.05$.

2.7.3. Correlation between behavioural and brain activity changes

Spearman's correlation coefficients were calculated between the changes after therapy for the behavioural test and the sensorimotor cortex activity, for each condition.

3. Results

After data acquisition, 3 children were excluded from the study because of inadequate quality of the neuroimaging data (see Appendix). Therefore, data for 26 children were used for all analyses.

3.1. Behavioural results

After therapy, the BBT score showed a trend of improvement on the MA hand (mean [SD] increase 1.04 [0.14] blocks; $P = 0.069$) and a significant increase in number of blocks transported with the LA hand (mean increase 2.44 [0.78] blocks; $P = 0.010$). The Manual Form Perception test score showed significant improvements in the MA hand (mean increase 0.64 [0.63]; $P = 0.042$), but not in the LA hand (mean increase 0.04 [0.53]; $P = 0.875$). Finally, the AHA score improved significantly (mean increase 1.91 [0.64] AHA-unit; $P = 0.007$) as did the ABILHAND-kids score (mean increase 1.19 [0.29] logits; $P < 0.001$).

3.2. Functional imaging results

3.2.1. Brain areas activated before and after HABIT-ILE

To identify the functional network that supported improvement in the motor task, all conditions were contrasted with the rest, before and after therapy separately (Table 1, Fig. 1). The contrast [(RCs1 + LCs1 + BCs1) > rest] before the intervention revealed a bilateral increase in brain activity in the cingulate gyrus, medial frontal gyrus (MeFG, supplementary motor area [SMA]), precentral gyrus (primary motor cortex [M1]) and postcentral gyrus (S1). Activation was also observed in the precentral gyrus (premotor cortex [PMC]), inferior parietal lobule (IPL) and cerebellum. In addition, the inferior frontal gyrus (IFG) of the right hemisphere was activated. The contrast [(RCs2 + LCs2 + BCs2) > rest] after the intervention showed activation in approximately the same regions observed before therapy. These results are congruent with the conjunction analysis, revealing as common areas activated for both conditions the cingulate gyrus and the MeFG, the precentral and postcentral

Table 1
Activation foci (positive values) before and after HABIT-ILE therapy.

Activation before therapy							
Brain region	Brodmann area	Cluster size	*t*-value	*P*-value	Talairach coordinates (x, y, z)		
L/R cingulate gyrus	BA 24	2094	5.64	0.000008	0	−1	45
L/R medial frontal gyrus	BA 6	1813	5.62	0.000009	0	−3	52
R precentral gyrus	BA 4	1700	5.70	0.000007	52	−10	43
R postcentral gyrus	BA 2,3	3269	6.95	0.000001	45	−28	54
R inferior parietal lobe	BA 40	1290	6.26	0.000002	39	−34	52
R precentral gyrus	BA 6	899	5.72	0.000007	31	−13	64
R precentral gyrus	BA 6	671	4.95	0.000047	55	−8	37
R inferior frontal gyrus	BA 44/6	1713	6.13	0.000003	57	8	7
R parietal lobe	BA 40	1823	4.58	0.000122	56	−20	16
R insula	BA 13	1397	5.25	0.000022	41	−4	0
R thalamus		762	5.66	0.000008	12	−19	7
R cerebellum		195	6.27	0.000002	14	−52	−17
L precentral gyrus	BA 4	710	5.25	0.000022	−36	−22	55
L postcentral gyrus	BA 2,3	772	5.42	0.000015	−32	−28	55
L cerebellum		1056	7.49	0.000001	−21	−49	−18
L precentral gyrus	BA 6	199	5.26	0.000022	−30	−20	60
L inferior parietal lobule	BA 40	492	5.19	0.000025	−35	−37	55
Activation after therapy							
L/R cingulate gyrus	BA24	379	5.34	0.000018	0	−1	46
L/R medial frontal gyrus	BA 6	1083	5.64	0.000008	0	−1	52
R precentral gyrus	BA 4	763	5.70	0.000007	51	−10	44
R postcentral gyrus	BA 2,3	2246	7.25	0.000001	46	−28	55
R inferior parietal lobe	BA 40	448	5.10	0.000032	39	−47	55
R precentral gyrus	BA 6	907	5.72	0.000007	30	−13	64
R precentral gyrus (*)	BA 6	101	5.58	0.000010	57	6	25
R inferior frontal gyrus	BA 44/6	501	6.13	0.000003	54	10	5
R thalamus		414	5.66	0.000008	12	−19	7
R cerebellum		1405	6.45	0.000001	12	−52	−17
R insula	BA 13	722	5.25	0.000024	42	2	3
L precentral gyrus	BA 4	846	5.95	0.000004	−35	−18	58
L postcentral gyrus	BA 2, 3	1096	5.76	0.000007	−39	−25	58
L cerebellum		1587	7.49	0.000001	−21	−49	−18
L inferior parietal lobe	BA 40	239	5.26	0.000022	−34	−39	55
L precentral gyrus	BA 6	171	5.35	0.000017	−30	−11	61
Conjunction analysis of the before and after therapy conditions							
L/R cingulate gyrus	BA24	317	4.32	0.000216	0	−1	46
L/R medial frontal gyrus	BA 6	545	4.88	0.000050	0	−10	55
R precentral gyrus	BA 6	630	5.00	0.000040	33	−13	62
R precentral gyrus	BA 4	660	5.28	0.000018	51	−13	43
R postcentral gyrus	BA 2,3	558	6.60	0.000001	42	−30	55
R parietal lobe	BA 40	404	4.55	0.000120	61	−22	22
L precentral gyrus	BA 4, 6	495	4.84	0.000056	−43	−22	55
L postcentral gyrus (*)	BA 2, 3	134	4.01	0.000482	−33	−28	58
L cerebellum		727	5.62	0.000007	−18	−49	−17

*Shown here for reference. Not significant after correction for cluster size.

gyrus, all of these bilaterally, as well as the parietal lobe of the right hemisphere and (left) cerebellum.

3.2.2. Brain areas modified after HABIT-ILE

The analysis to evaluate the brain activity changes in the right-hand condition [(RCs2 > rest) minus (RCs1 > rest)] indicated significant increases in activation of the left hemisphere of the middle frontal gyrus (MiFG), PMC and M1, as well as cingulate gyrus. In addition, in the right hemisphere, activation was decreased in the PMC and M1 and increased in the superior frontal gyrus (SFG), MiFG and precuneus (Table 2, Fig. 2).

In the left-hand condition [(LCs2 > rest) minus (LCs1 > rest)], we observed a significant bilateral increase in activation within the MiFG, IPL and cingulate gyrus, as well as an increase in the globus pallidus in the right hemisphere. In addition, activation was decreased in the left hemisphere of M1, S1, PMC, IFG and putamen (Table 3, Fig. 2).

The analysis for the both-hands condition [(BCs2 > rest) minus (BCs1 > rest)] showed significantly increased activation in the bilateral cingulate gyrus, MeFG, superior parietal lobe and thalamus. In addition, we found unilateral increased activation in MiFG and cerebellum of the right hemisphere as well as M1, PMC, IFG, and SFG (Table 4, Fig. 2).

3.2.3. Correlation between changes in behavioural assessment and sensorimotor brain activity changes

Changes in sensorimotor areas were not uniform in all children: some showed an increase in activation and some a decrease in activation. In the LC, the non-lesional hemisphere changes in brain activity were correlated with the ABILHAND-kids score ($r = -0.65$, $P < 0.001$), with a trend in correlation with the BBT score ($r = -0.39$, $P = 0.052$). In the RC, we observed a trend for correlation with the ABILHAND-kids score ($r = -0.38$, $P = 0.057$) and in the BC, a correlation with the ABILHAND-kids score ($r = -0.65$, $P < 0.001$). No other associations were detected. Of note, when observing these correlations, children with a decrease in brain activity after therapy showed greater improvements than those with an increase in brain activity after therapy (Fig. 2).

4. Discussion

This study aimed to investigate the brain activation changes induced by HABIT-ILE on the cortical network related to motor learning and to correlate these changes with functional assessments in children with USCP. We found activation of an overlapping fronto-parietal network also involving the cerebellum

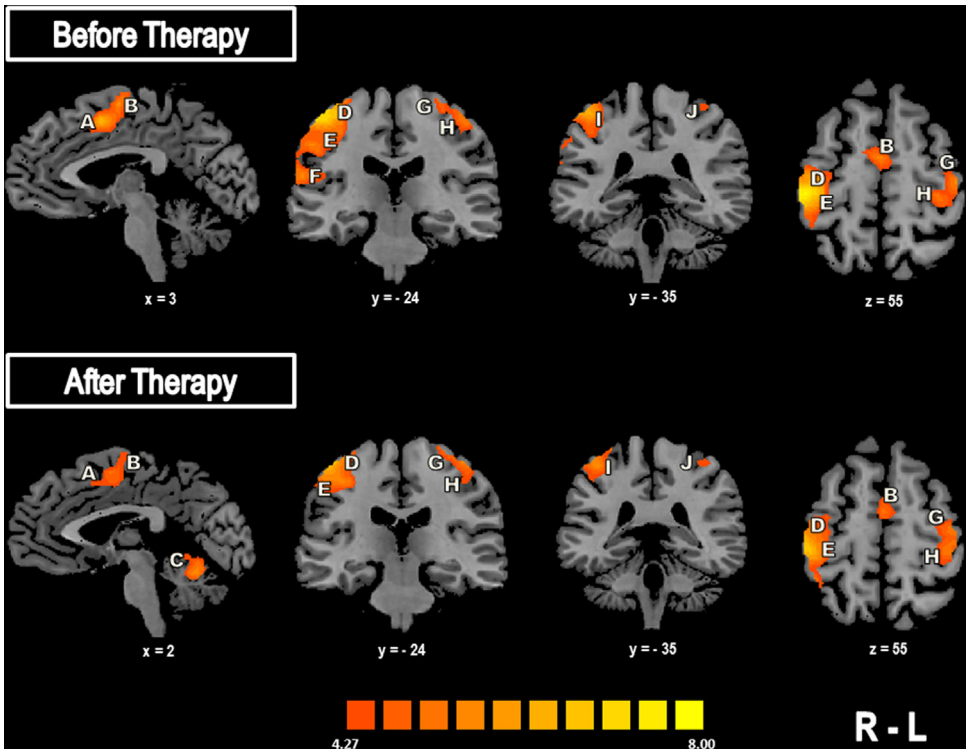

Fig. 1. Brain activation maps before and after therapy. Regions activated by task performance in the contrast [(RCs1 + LCs1 + BCs1) > rest] and [(RCs2 + LCs2 + BCs2) > rest] are separately displayed according to color scales that encode the activation level based on *t*-statistic values. A. Anterior cingulate gyrus (BA 24). B. Medial frontal gyrus (or SMA, BA 6). C. Right cerebellum. D. Right precentral gyrus (or M1, BA 4). E. Right postcentral gyrus (or S1, BA 2,3). F. Right postcentral gyrus (BA 40). G. Left precentral gyrus (or M1, BA 4). H. Left postcentral gyrus (BA 2,3). I. Right inferior parietal lobule (BA 40). J. Left inferior parietal lobule (BA 40). L: left; R: right; BA: Brodmann area; SMA: supplementary motor area; MI: primary motor cortex; SI: postcentral gyrus.

Table 2
Activation foci modified after HABIT-ILE therapy.

Brain region	Brodmann area	Cluster size	*t*-value	*P*-value	Talairach coordinates (x, y, z)		
L middle frontal gyrus	BA 9	250	3.69	0.000222	−36	8	49
L precentral gyrus	BA 4,6	187	3.67	0.000248	−54	−1	32
L middle frontal gyrus	BA 46	623	4.00	0.000064	−18	41	13
L cingulate gyrus	BA 30	869	4.29	0.000018	−12	−43	7
L cingulate gyrus	BA 31	824	4.51	0.000007	−12	−55	28
R precentral gyrus	BA 4, 6	246	−4.14	0.000035	55	−6	28
R precentral gyrus	BA 44,6	421	−4.15	0.000034	45	−4	12
R superior frontal gyrus	BA 6, 8	387	4.08	0.000045	21	38	46
R/L middle frontal gyrus	BA 9	848	4.28	0.000019	−3	44	31
R precuneus	BA 7	735	4.48	0.000008	0	−46	55

More affected hand condition [(RCs2 > rest) minus (RCs1 > rest)].

before and after therapy. After the intervention, when the task was performed with the more-affected hand, activity was decreased on the motor cortex of the non-lesional hemisphere and increased in motor areas of the lesional hemisphere. Otherwise, when the task was performed with the less-affected hand, changes were mainly in the non-affected hemisphere, with a decrease in activity of the sensorimotor areas. When the task was performed with both hands, activity of both hemispheres was increased.

Previous CIMT or bimanual therapy studies described overall increased activation of the primary motor cortex after intervention, mainly confined to the lesional hemisphere, but also extending to the non-lesional hemisphere [13,28]. Because intensive therapies are based on motor skill learning principles [3–5], the differences observed in the brain activation after the intervention may be linked to ultrastructural changes underlying the motor learning. These changes may include modifications in the dendritic architecture or synaptic strength [29]. Moreover, a recent report showed such neuronal connectivity changes in rats with a focal motor cortex lesion after an intensive intervention model [30].

The activation pattern observed before and after HABIT-ILE encompassed an extensive network of fronto-parietal cortex and cerebellum that supports motor skill learning [10,11,31]. The M1 controls volitional movements [32] and may be modified by sensory feedbacks [33] from somatosensory areas, such as the S1 [34] and the parietal cortex, in our case, the IPL (Brodmann area [BA] 40), relevant for sensorimotor integration, thus contributing to motor control [35]. In addition, we observed activation of the SMA, associated with the prefrontal cortex, and the M1 [10,31], associated with movement planning [31]. Furthermore, we found activation of the premotor cortex involved in the selection and initiation of voluntary movements, associated with the M1 [36]. Finally, the cerebellum activation we observed could be associated with motor skill adaptations regarding the environment

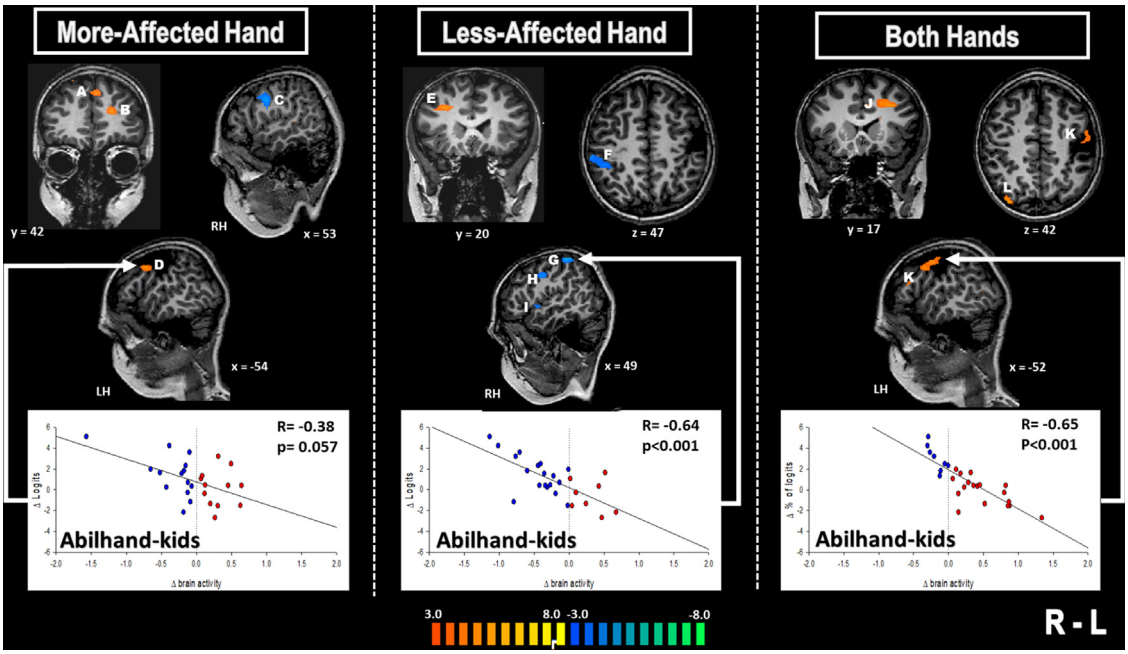

Fig. 2. Brain activation maps after therapy in each condition. Regions with task-dependent activation before therapy [(RCs2 > rest) minus (RCs1 > rest)], [(LCs2 > rest) minus (LCs1 > rest)] and [(BCs2 > rest) minus (BCs1 > rest)] are displayed separately with color scales encoding the activation level as *t*-statistic values. A. Right and left middle frontal gyrus (BA 9). B. Left middle frontal gyrus (BA 46). C. Right precentral gyrus (BA 4, 6). D. Left precentral gyrus (BA 4, 6). E. Right middle frontal gyrus (BA 9). F. Right postcentral gyrus (BA 1, 2, 3). G. Right precentral gyrus (BA 4). H. Right precentral gyrus (BA 6). I. Inferior frontal gyrus (BA 44, 6). J. Left medial frontal gyrus (BA 9). K. Left precentral gyrus (BA 4, 6). L. Right superior parietal lobe (BA 7). L: left; R: right; RH: right hemisphere; LH: left hemisphere.

Table 3
Activation foci modified after HABIT-ILE therapy.

Brain region	Brodmann area	Cluster size	*t*-value	*P*-value	Talairach coordinates (x, y, z)		
R precentral gyrus	BA 4	234	−3.83	0.000013	36	−24	55
R postcentral gyrus	BA 1, 2, 3	1513	−4.98	0.000001	43	−31	50
R precentral gyrus	BA 6	687	−4.92	0.000001	55	−1	31
R middle frontal gyrus	BA 9	1000	4.20	0.000026	30	20	28
R putamen		765	−4.14	0.000034	18	−7	13
R globus pallidus		270	4.24	0.000022	12	2	4
R inferior frontal gyrus	BA 44, 6	960	−5.40	0.000001	42	−7	13
R inferior parietal lobe	BA 39, 40	285	3.92	0.00009	33	−67	31
R cingulate gyrus	BA 31	725	4.53	0.000006	9	−55	25
L middle frontal gyrus	BA 9	239	4.20	0.000027	−21	41	16
L inferior parietal lobe	BA 39, 40	201	3.45	0.000553	−40	−64	25
L posterior cingulate gyrus	BA 31	368	3.82	0.000136	−12	−55	28

Less affected hand condition [(LCs2 > rest) minus (LCs1 > rest)].

[6]. Thus, the activation of this network we observed demonstrates that although children with USCP show an important reorganisation following the brain lesion [13], the regions involved in the motor skill learning process are similar to the cortical network observed in adults without lesions [10,11].

The changes we observed in the brain network could highlight improvements in the motor performance related to a better motor execution involving the premotor cortex, SMA, and M1 [37]. Although not directly evaluated, other processes possibly improved owing to changes in a whole network are motor planning, associated with activation in the SMA, parietal cortex, PMC and prefrontal cortex, and the use of attentional resources, related mainly to the prefrontal cortex such as the dorsolateral prefrontal cortex [37].

4.1. Activation changes induced by intensive therapy

From a global point of view, we observed changes in the brain activity in both hemispheres when the task was performed with the more-affected and both hands, but mainly in the non-lesional hemisphere when the task was performed with the less-affected hand. In addition, in the correlation analysis, we observed a difference in the improvement between children with increased or decreased activity after therapy.

One hypothesis explaining the changes observed after the intervention in each condition might be an improvement in the interhemispheric inhibition imbalance [38]. Indeed, in children with CP, a higher interhemispheric inhibitory imbalance has been associated with worse motor performance [39]. In this study, the brain activity changes observed mainly during the unimanual conditions, with a decrease in the brain activity of the non-lesional hemisphere after therapy, could be interpreted as a reduction in the degree of inhibition exerted by the lesioned hemisphere and could have contributed to the better motor performances observed after therapy.

Concerning the activation level of the lesional hemisphere, previous studies have associated the behavioural response to intensive rehabilitation treatments with a reorganisation of the

Table 4
Activation foci modified after HABIT-ILE therapy.

Brain region	Brodmann area	Cluster size	*t*-value	*P*-value	Talairach coordinates (x, y, z)		
R middle frontal gyrus	BA 9	686	5.25	0.000001	21	26	34
R medial frontal gyrus	BA 9	279	4.07	0.000047	15	41	19
R superior parietal lobe	BA 7	326	4.92	0.000001	30	−73	40
R cingulate gyrus	BA 31	724	4.96	0.000001	18	−46	28
R thalamus		379	5.71	0.000001	12	−1	4
R cerebellum		782	4.63	0.000004	27	−68	−14
L precentral gyrus	BA 4, 6	1206	4.94	0.000001	−48	−7	47
L medial frontal gyrus	BA 9	2947	5.14	0.000001	−18	23	34
L inferior frontal gyrus	BA 44, 46	471	4.60	0.000004	−48	26	13
L superior frontal gyrus	BA 6, 8	4416	5.22	0.000001	−33	44	19
L superior parietal lobe	BA 7	2510	5.23	0.000001	−18	−37	52
L middle temporal gyrus	BA 39	296	4.17	0.000031	−45	−58	7
L cingulate gyrus	BA 31	1300	4.46	0.000008	−21	−49	34
L thalamus		207	4.49	0.000007	−15	−31	10

Both hands condition [(BCs2 > rest) minus (BCs1 > rest)].

corticospinal tract [14]. Those studies also described two types of treatment-related neuroplasticity: increased activation and excitability in the sensorimotor cortex of the lesional hemisphere in children with ipsilateral reorganisation or decreased activation in this same area in children with contralateral reorganisation [14,40]. Weinstein et al. [28], in a study of neuroplastic changes associated with intensive bimanual therapy in children, observed increased activation levels regardless of whether the task was performed with the less or more affected hand.

In addition, we observed an association between the changes after therapy in behavioural assessment and brain activity changes in the motor cortex obtained by contrasting the brain activity after and before the intervention. In this correlation, children with decreased activity after therapy showed more improvements than children with increased activity after therapy. The correlation with the motor cortex is important because of the critical role of this region in the execution of volitional movement of the upper extremity and the later output to the spinal cord through the corticospinal tract [41]. This difference probably highlights two different steps of the rehabilitation process. In line with this hypothesis, Steele and Penhune [12] described a biphasic acquisition of motor skill learning in healthy individuals, in whom brain activation first increases while learning a new task but subsequently declines upon mastery of the task. As the process becomes more efficient, the involved brain regions become more focused. Therefore, a decrease in the brain activity with greater improvement in functional measurements would correspond to a decrease in brain activation (see Fig. 2), probably indicating a refinement of the cortical substrates leading to better performance of the motor skill. Similarly, studies of changes in gray matter volume showed that the skill acquisition involves an initial phase, with an increase in gray matter volume, followed by a decrease of this matter related to a plateau of the behavioural performance. These macroscopic changes have been associated with cellular changes including neurogenesis, synaptic changes, and changes in the glial cells [42].

In addition, we observed an increase in the activation of other similar regions during the different conditions, which suggests that the motor learning process followed during the intervention involves not only motor changes, but also other mechanisms related to the motor function. The non-specific motor regions activated were mainly in the prefrontal cortex (BA 8, 9, 46), which are widely connected with motor areas and involve cognitive control and motor planning [43]. In addition, we observed activation in the parietal cortex (BA 7, 39, 40), which are related to sensorimotor integration [44]. These areas of the parietal cortex are also functionally connected with the PMC and prefrontal cortex. An increase in activity of the posterior cingulate cortex (BA 30, 31) was also observed. These areas are connected to the prefrontal cortex and have been related to control of attention [45].

Besides the results presented, this study could present some bias. In general, the manipulation of objects during fMRI may induce movement artifacts on the images acquired. Despite verifying the head movement and performing movement corrections, we cannot completely exclude some influence of these artefacts during the data analyses. Because of the before–after design, we cannot rule out the possibility of brain plasticity changes due to development. This topic could be studied in the future with these analyses performed between children with CP and a control group.

5. Conclusion

Brain activation changes were observed in an extensive fronto-parietal and cerebellum network that underlies the motor skill learning upon HABIT-ILE in children with USCP. Two different patterns were observed, probably representing different phases of functional recovery. These two patterns might indicate an increased practice-dependent brain recruitment or a refinement of brain activation by more efficient means. Future studies should investigate the role of the different network regions involved in these phases of the rehabilitation process and their implications for targeted interventions.

Authors' contributions

RA participated in data collection, data analysis and writing; LD participated in the project design, data collection, data analysis and writing; DE-K participated in data collection and writing; JP participated in recruitment, data collection and writing; AG participated in the project design and writing; KF participated in the project design and writing; YB participated in the project design, recruitment, data collection, data analysis and writing.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rehab.2021.101502.

References

[1] Graham HK, Rosenbaum P, Paneth N, Dan B, Lin J-P, Damiano DL, et al. Cerebral palsy. Nat Rev Dis Primers 2016;2:16005.
[2] Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. Dev Med Child Neurol 2013;55:885–910.
[3] Eliasson AC, Krumlinde-sundholm L, Shaw K, Wang C. Effects of constraint-induced movement therapy in young children with hemiplegic cerebral palsy: an adapted model. Dev Med Child Neurol 2005;47:266–75.
[4] Gordon AM, Schneider JA, Chinnan A, Charles JR. Efficacy of a hand-arm bimanual intensive therapy (HABIT) in children with hemiplegic cerebral palsy: a randomised control trial. Dev Med Child Neurol 2007;49:830–8.
[5] Bleyenheuft Y, Arnould C, Brandao MB, Bleyenheuft C, Gordon AM. Hand and arm bimanual intensive therapy including lower extremity (HABIT-ILE) in children with unilateral spastic cerebral palsy: a randomised trial. Neurorehabil Neural Repair 2015;29:645–57.
[6] Doyon J, Ungerleider LG. Functional anatomy of motor skill learning. In: Squire LS, Schacter DL, editors. Neuropsychology of memory. New York: Guilford Press; 2002.
[7] Kleim JA, Hogg TM, VandenBerg PM, Cooper NR, Bruneau R, Remple M. Cortical synaptogenesis and motor map reorganisation occur during late, but not early, phase of motor skill learning. J Neurosci 2004;24:628–33.
[8] Sale MV, Reid LB, Cocchi L, Pagnozzi AM, Rose SE, Mattingley JB. Brain changes following four weeks of unimanual motor training: evidence from behaviour, neural stimulation, cortical thickness, and functional MRI. Hum Brain Mapp 2017;38:4773–87.
[9] Ljubisavljevic M. Transcranial magnetic stimulation and the motor learning-associated cortical plasticity. Exp Brain Res 2006;173:215–22.
[10] Ungerleider LG, Doyon J, Karni A. Imaging brain plasticity during motor skill learning. Neurobiol Learn Mem 2002;78:553–64.
[11] Dayan E, Cohen LG. Neuroplasticity subserving motor skill learning. Neuron 2011;72:443–54.
[12] Steele CJ, Penhune VB. Specific increases within global decreases: a functional magnetic resonance imaging investigation of five days of motor sequence learning. J Neurosci 2010;30:8332–41.
[13] Inguaggiato E, Sgandurra G, Perazza S, Guzzetta A, Cioni G. Brain reorganisation following intervention in children with congenital hemiplegia: a systematic review. Neural Plast 2013;2013:356275.
[14] Juenger H, Kuhnke N, Braun C, Ummenhofer F, Wilke M, Walther M, et al. Two types of exercise-induced neuroplasticity in congenital hemiparesis: a transcranial magnetic stimulation, functional MRI, and magnetoencephalography study. Dev Med Child Neurol 2013;55:941–51.
[15] Reid LB, Rose SE, Boyd RN. Rehabilitation and neuroplasticity in children with unilateral cerebral palsy. Nat Rev Neurol 2015;11:390–400.
[16] Nichols TE, Das S, Eickhoff SB, Evans AC, Glatard T, Hanke M, et al. Best practices in data analysis and sharing in neuroimaging using MRI. Nat Neurosci 2017;20:299–303.
[17] Eliasson AC, Krumlinde-Sundholm L, Rosblad B, Beckung E, Arner M, Ohrvall AM, et al. The manual ability classification system (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. Dev Med Child Neurol 2006;48:549–54.
[18] Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214–23.
[19] Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. Dev Med Child Neurol 2007;49:144–51.
[20] Bleyenheuft Y, Dricot L, Ebner-Karestinos D, Paradis J, Saussez G, Renders A, et al. Motor skill training may restore impaired corticospinal tract fibres in children with cerebral palsy. Neurorehabil Neural Repair 2020 [1545968320918841].
[21] Bleyenheuft Y, Gordon AM. Hand-arm bimanual intensive therapy including lower extremities (HABIT-ILE) for children with cerebral palsy. Phys Occup Ther Pediatr 2014;34:390–403.
[22] Mathiowetz V, Volland G, Kashman N, Weber K. Adult norms for the Box and Block Test of manual dexterity. Am J Occup Ther 1985;39:386–91.
[23] Cooper J, Majnemer A, Rosenblatt B, Birnbaum R. The determination of sensory deficits in children with hemiplegic cerebral palsy. J Child Neurol 1995;10:300–9.
[24] Arnould C, Penta M, Renders A, Thonnard JL. ABILHAND-Kids: a measure of manual ability in children with cerebral palsy. Neurology 2004;63:1045–52.
[25] Krumlinde-sundholm L, Eliasson A-C. Development of the assisting hand assessment: a Rasch-built measure intended for children with unilateral upper limb impairments. Scand J Occup Ther 2003;10:16–26.
[26] Friston KJ, Holmes AP, Price CJ, Buchel C, Worsley KJ. Multisubject fMRI studies and conjunction analyses. Neuroimage 1999;10:385–96.
[27] Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med 1995;33:636–47.
[28] Weinstein M, Myers V, Green D, Schertz M, Shiran SI, Geva R, et al. Brain plasticity following intensive bimanual therapy in children with hemiparesis: preliminary evidence. Neural Plast 2015;2015:798481.
[29] Zatorre RJ, Fields RD, Johansen-Berg H. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat Neurosci 2012;15:528–36.
[30] Wang L, Conner JM, Nagahara AH, Tuszynski MH. Rehabilitation drives enhancement of neuronal structure in functionally relevant neuronal subsets. Proc Natl Acad Sci U S A 2016;113:2750–5.
[31] Ashe J, Lungu OV, Basford AT, Lu X. Cortical control of motor sequences. Curr Opin Neurobiol 2006;16:213–21.
[32] Liuzzi G, Horniss V, Zimerman M, Gerloff C, Hummel FC. Coordination of uncoupled bimanual movements by strictly timed interhemispheric connectivity. J Neurosci 2011;31:9111–7.
[33] Nudo RJ. Recovery after brain injury: mechanisms and principles. Front Hum Neurosci 2013;7:887.
[34] Salinas E, Romo R. Conversion of sensory signals into motor commands in primary motor cortex. J Neurosci 1998;18:499–511.
[35] Ostry DJ, Gribble PL. Sensory plasticity in human motor learning. Trends Neurosci 2016;39:114–23.
[36] Cisek P, Kalaska JF. Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. Neuron 2005;45:801–14.
[37] Omata K, Ito S, Takata Y, Ouchi Y. Similar neural correlates of planning and execution to inhibit continuing actions. Front Neurosci 2018;12:951.
[38] Takeuchi N, Oouchida Y, Izumi S. Motor control and neural plasticity through interhemispheric interactions. Neural Plast 2012;2012:823285.
[39] Ciechanski P, Zewdie E, Kirton A. Developmental profile of motor cortex transcallosal inhibition in children and adolescents. J Neurophysiol 2017;118:140–8.
[40] Kuhnke N, Juenger H, Walther M, Berweck S, Mall V, Staudt M. Do patients with congenital hemiparesis and ipsilateral corticospinal projections respond differently to constraint-induced movement therapy? Dev Med Child Neurol 2008;50:898–903.
[41] Edwards LL, King EM, Buetefisch CM, Borich MR. Putting the "sensory" into sensorimotor control: the role of sensorimotor integration in goal-directed hand movements after stroke. Front Integr Neurosci 2019;13:16.
[42] Wenger E, Brozzoli C, Lindenberger U, Lovden M. Expansion and renormalisation of human brain structure during skill acquisition. Trends Cogn Sci 2017;21:930–9.
[43] Hasan A, Galea JM, Casula EP, Falkai P, Bestmann S, Rothwell JC. Muscle and timing-specific functional connectivity between the dorsolateral prefrontal cortex and the primary motor cortex. J Cogn Neurosci 2013;25:558–70.
[44] Haines DE, Mihailoff GA, Cunningham WK, Schenk MP, Armstrong GW, Runyan CP. Fundamental neuroscience for basic and clinical applications; 2018.
[45] Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. Brain 2014;137:12–32.