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FUNCTIONAL MAGNETIC RESONANCE EVIDENCE OF CORTICAL ALTERATIONS IN A CASE OF REVERSIBLE CONGENITAL LYMPHEDEMA OF THE LOWER LIMB: A PILOT STUDY

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ABSTRACT

We report the first application of brain functional Magnetic Resonance Imaging (fMRI) to congenital peripheral lymphedema patients before and after microsurgical treatment. Our aim was to evaluate the effects of limb shape change on cortical organization of the motor system and how the cortical sensorimotor network restructures after microsurgical therapy. We acquired fMRI during active motor and motor imagery tasks before surgery and six months after surgery in a patient with congenital lymphedema of the left leg. fMRI data revealed activation differences in primary and secondary motor areas between the two scanning sessions for both tasks and also between the patient's and a healthy volunteer's activations. We suggest that these alterations could be related to changes in body schema representation due to the congenital lymphedema.

Keywords: lymphedema, functional Magnetic Resonance Imaging, brain plasticity, sensorimotor cortex

Peripheral lymphedema is the accumulation of lymph in the interstitial spaces caused by the failure of the lymph vascular system to accept and conduct lymph back to the blood circulation resulting in a chronic and disabling condition characterized by progressive volume increase of the involved limbs, elephantiasis, skin hyperkeratosis and functional impairment.

The prevalence of lymphedema worldwide is approximately one hundred forty million people (1), the vast majority with the acquired form rather than the relatively much rarer congenital type. Subjects with lymphedema usually complain of subjective sensory alterations such as tingling, aching or heaviness in the affected limb but do not present focal motor deficits or force loss.

Microsurgical procedures for peripheral lymphedema are divided into reconstructive and derivative methods; derivative lymphatic-venous microsurgery usually consists of multiple lymphatic-venous anastomoses that allow the lymph to flow freely into the venous circulation (2)

Brain functional Magnetic Resonance Imaging (fMRI) uses variation of the signal due to alterations in local concentration of deoxygenated hemoglobin (3) to indirectly evaluate regional brain activity (4): fMRI has been extensively utilized to shed light on the motor, sensory and cognitive systems of the human brain (5).

In this study, we used a simple motor task to probe the cortical motor representation of the affected limb in order to evaluate the effects of mono-lateral congenital lymphedema and of the surgical treatment on motor system architecture and functions.

As patients with this condition present with a congenital pure mechanical deficit that does not directly affect the nervous system, and that can at times be resolved with surgery, we believed this could be an interesting model to study the re-organization of the human sensory-motor system due to alterations in limb shape and conformation.

To our knowledge, this is the first report of the application of functional imaging techniques and paradigms to investigate the effects of congenital lymphatic disease on the central nervous system and the effects of surgical treatment of this disorder.

MATERIALS AND METHODS

Subject

A 30-year-old female with congenital lymphedema of the left lower limb was selected for derivative lymphatic-venous microsurgery. Her physical examination revealed late stage 2 lymphedema of the left leg, with moderate volume difference between the two legs. Lower limb lymphoscintigraphy performed before surgery showed very low inguinal lymph node tracer uptake and significant dermal back flow and confirmed lymphatic insufficiency in the left leg. Her clinical examination was otherwise unremarkable, and she did not present any objective motor or sensory deficit to the affected leg. After approval from the Hospital Ethics Committee, the patient underwent brain fMRI one week before and six months after surgery.

Upon discharge from the hospital, the patient did not enroll in any physiotherapeutic protocols, however, she continued to wear an elastic support garment during the day. Post-surgical clinical evaluation of the left leg showed a 70% excess volume reduction and a normalization of the lymphangioscintigraphic findings with evident preferential lymphatic pathways and a reduction of dermal back flow.

Surgical Procedure

Derivative lymphatic-venous microsurgery was performed as described elsewhere (2). Briefly, anastomoses were performed both end-to-end and end-to-side. The end-to-end procedure was carried out by means of a telescopic method with a single U-shaped stitch, anastomosing lymphatic collectors to a continent venous secondary branch. End-to-side lymphatic-venous anastomoses were performed by using the outlet of a collateral venous branch as entry hole for lymphatic vessels.

Tasks Description

The patient was asked to perform two tasks: a simple active motor task and a kinesthetic motor imagery task (MI). In the active motor task, the subject performed a metronome-paced (1.5 Hz) flexion-extension of the toes of the left foot for 30 seconds ("active motor condition") followed by 30 seconds of inactivity ("rest condition") while in the MI condition, the patient had to imagine performing the same movement for 30 seconds ("imagery condition") or to rest for 30 seconds ("rest condition") without making any overt movement. The subject practiced the task for five minutes outside the scanner both one day before the scanning session and just before entering the scanner for each of the two sessions; we also evaluated the number of motor acts to control for differences in performance during both the training sessions and the fMRI acquisitions. During the pre-surgery and the post-surgery imaging sessions, each condition was repeated four times divided into two runs. On both occasions, the patient was asked to quantify on a scale from one to ten how difficult she found the task and if she perceived any differences between the two runs. A healthy

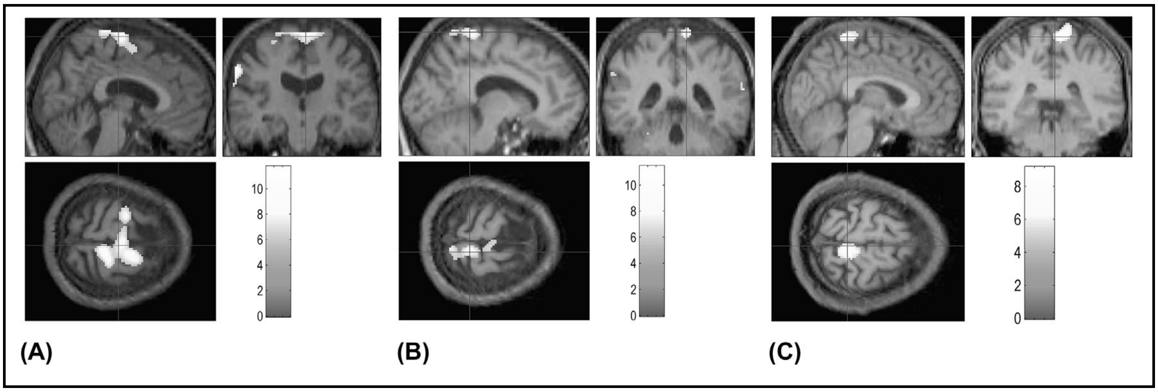

Fig 1. Task-specific activation maps (P< 0.001). (A) pre-surgery session; (B) post-surgery session; (C) healthy control.

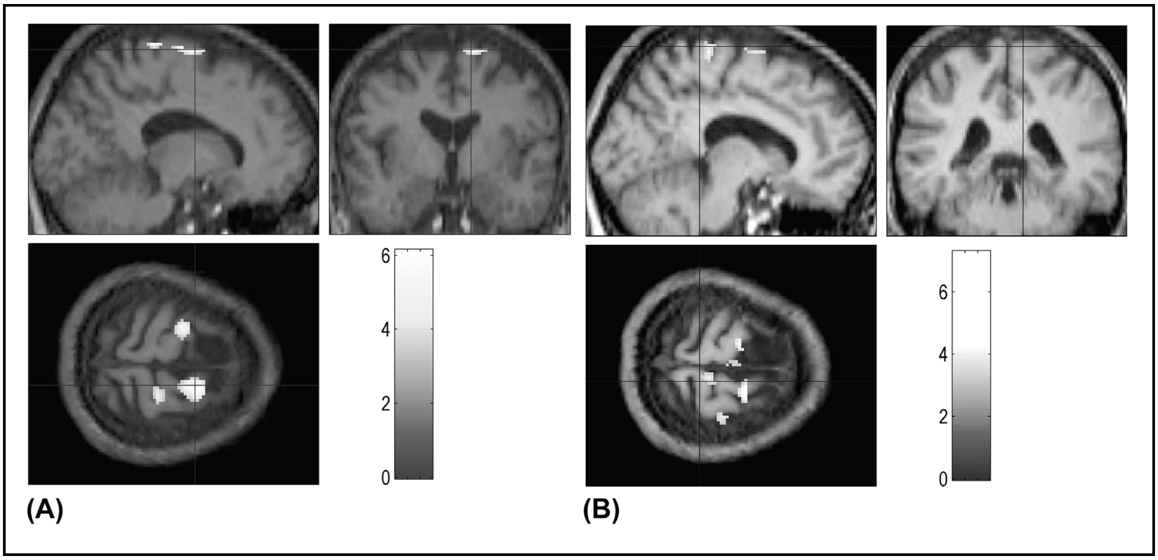

Fig 2. Statistical contrasts between the pre-surgery and post-surgery conditions activation maps for the active motor (A) and motor imagery (B) tasks.

age- and sex-matched volunteer underwent the same imaging protocol (both time points) for the active task only.

Image Acquisition and Analyses

Images were acquired on a 1.5 T scanner (General Electric, Milwaukee, WI, USA). High-resolution anatomical images were acquired using a 3D SPGR sequence (TR = 30 ms; TE = 3 ms; slice thickness = 3 mm; FOV = 240 mm; Matrix: 256x256; Flip Angle = 35°). The functional images were acquired using echo-planar imaging (EPI) sequences to obtain 23 contiguous slices for each brain volume (TR = 3000 ms; TE = 40 ms; FOV = 260 mm; Matrix=64 X 64; slice thickness = 5mm).

We acquired 43 brain volumes for each of the two runs; the first 3 volumes in each session were discarded to allow for initial T1 equilibrium effects. The remaining volumes were analyzed with SPM2 (Wellcome Department of Cognitive Neurology, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 6 (Mathworks, Inc., Sherborn , MA, USA) as described elsewhere (4,6). Briefly, the images were realigned to the first image acquired for each task, and a mean functional image was created. Then the mean functional images for pre- and post-surgery sessions were normalized to the Montreal Neurological Institute (MNI) brain template, and the resulting transformation matrix was applied to all the functional images. Finally, the images were smoothed with an 8-8-10 mm FWHM Gaussian kernel. Statistical analyses were performed using the General Linear Model (7). Activations surviving a threshold of $P < 0.001$ uncorrected were considered statistically significant.

RESULTS

Analysis of task-specific activations during the pre-surgery active motor task revealed activation peaks in the right primary motor and in the left and right secondary motor areas *(Fig. 1a*), while in the post-surgery imaging session the activation peaks were in the right primary motor and in only the right secondary motor area (*Fig. 1b*).

We then ran the pre-surgery vs. post-surgery statistical contrast for both the MI and the active motor task. In the pre-surgery session, we found during both tasks significantly active voxels in the right primary motor and in the left and right secondary motor areas (*Fig. 2*) that did not reach significant activation in the post-surgery session. Activation patterns for both contrasts showed a significant overlap in bilateral supplementary motor area. Moreover, in the MI pre-post contrast, we found activations in the primary motor cortex (synopsis of brain activations in *Table 1*).

Task-specific activation map analysis in an age-matched healthy volunteer revealed a significant cluster only in the right primary motor cortex during both scanning sessions (*Fig. 1c*).

DISCUSSION

The aim of this study was to explore the nature of adaptive motor cortex plasticity due to primary lymphedema and the ability of a successful microsurgical lymphatic-venous shunt to modify this condition.

We found over-activations during the active motor task in the pre-surgery scan compared both to the post-surgery scan and the normal control data. Moreover, the pre-compared to the post- statistical contrasts both for the motor imagery and the active motor task showed co-localized activation patterns in ipsilateral and controlateral supplementary motor areas.

Different factors modulate cortical activations during a motor task: previous studies showed that there is a positive relationship among the recruitment pattern of motor areas, the extent of the activations, and the kinematic properties of a motor task such as the movement rate (8). However, we think that our findings cannot be explained by a simple alteration in cinematic properties of the motor task as the alterations in activation patterns were also present in the motor imagery task. Moreover, the patient did not perceive any differences in task difficulty as assessed by pre- and post-surgery scores on our task evaluation scale.

Another possible confounding factor could be a difference in familiarity (9) with the tasks between the two scanning sessions. However, we think this issue is not relevant in this case given the protracted training outside the scanner also before the first session and the lack of differences in activations at the two time points in the normal control data.

An enlarged pattern of cortical motor activations similar to the pattern found in the pre-surgery imaging session has been described in patients with motor neuropathy (10) during a hand movement task. In that patient group, functional plasticity has been linked with disinhibition of latent intracortical connections.

TABLE 1
Brain Activations for the Active Motor and Motor Imagery Tasks

coordinates			Anatomical Localization			voxel	voxel
x	y	z			Broadman Area	T	equivZ
Active motor task – pre-surgery							
-65	-24	33	Left Cerebrum	Postcentral Gyrus	B.A. 2	11.74	Inf
-65	-7	22	Left Cerebrum	Precentral Gyrus	B.A. 4	9.47	Inf
-61	3	29	Left Cerebrum	Precentral Gyrus	B.A. 6	7.75	7.37
14	-28	70	Right Cerebrum	Precentral Gyrus	B.A. 4	11.57	Inf
14	-3	65	Right Cerebrum	Superior Frontal Gyrus	B.A. 6	11.36	Inf
-20	-12	67	Left Cerebrum	Superior Frontal Gyrus	B.A. 6	10.04	Inf
-24	-38	-22	Left Cerebrum	Fusiform Gyrus	B.A. 20	6.9	6.63
-32	-44	-20	Left Cerebrum	Fusiform Gyrus	B.A. 20	6.25	6.04
63	13	21	Right Cerebrum	Inferior Frontal Gyrus	B.A. 45	6.82	6.56
57	15	-6	Right Cerebrum	Superior Temporal Gyrus	B.A. 38	6.68	6.43
59	12	1	Right Cerebrum	Superior Temporal Gyrus	B.A. 22	6.31	6.09
67	-14	27	Right Cerebrum	Postcentral Gyrus	B.A. 1	6.06	5.87
65	-31	35	Right Cerebrum	Inferior Parietal Lobule	B.A. 40	6.03	5.85
-4	21	36	Left Cerebrum	Cingulate Gyrus	B.A. 32	5.94	5.76
42	-7	59	Right Cerebrum	Precentral Gyrus	B.A. 6	5.83	5.65
36	-18	64	Right Cerebrum	Precentral Gyrus	B.A. 6	5.26	5.13
8	10	46	Right Cerebrum	Medial Frontal Gyrus	B.A. 32	5.05	4.93
-26	32	24	Left Cerebrum	Middle Frontal Gyrus	B.A. 9	4.99	4.88
Active motor task – pre-surgery/post-surgery contrast							
-64	6	14	Left Cerebrum	Precentral Gyrus	B.A. 6	11.42	Inf
-64	2	22	Left Cerebrum	Precentral Gyrus	B.A. 6	10.59	Inf
-62	2	34	Left Cerebrum	Precentral Gyrus	B.A. 6	10.2	Inf
-62	4	26	Left Cerebrum	Precentral Gyrus	B.A. 6	10	Inf
-66	-20	28	Left Cerebrum	Postcentral Gyrus	B.A. 2	6.98	6.7
-66	-10	26	Left Cerebrum	Precentral Gyrus	B.A. 4	6.3	6.09
60	14	4	Right Cerebrum	Precentral Gyrus	B.A. 44	9.15	Inf
68	-16	20	Right Cerebrum	Postcentral Gyrus	B.A. 43	8.95	Inf
62	6	22	Right Cerebrum	Inferior Frontal Gyrus	B.A. 9	8.26	7.79
10	-40	70	Right Cerebrum	Paracentral Lobule	B.A. 4	8.71	Inf
12	-56	72	Right Cerebrum	Postcentral Gyrus	B.A. 7	6.25	6.04
0	-10	62	Left Cerebrum	Medial Frontal Gyrus	B.A. 6	8.22	7.76
6	-10	62	Right Cerebrum	Medial Frontal Gyrus	B.A. 6	7.69	7.32
-50	-12	56	Left Cerebrum	Precentral Gyrus	B.A. 4	6.75	6.49
-46	-14	60	Left Cerebrum	Postcentral Gyrus	B.A. 3	5.85	5.67
44	-8	64	Right Cerebrum	Precentral Gyrus	B.A. 6	6.58	6.34
-34	-14	68	Left Cerebrum	Precentral Gyrus	B.A. 6	5.95	5.77
Active motor task – normal control							
8	-38	65	Right Cerebrum	Paracentral Lobule	B.A. 4	8.19	7.4
-53	-19	16	Left Cerebrum	Postcentral Gyrus	B.A. 43	6.24	5.85
Active motor task – post-surgery							
-63	6	13	Left Cerebrum	Precentral Gyrus	B.A. 6	11.42	Inf
-61	4	31	Left Cerebrum	Precentral Gyrus	B.A. 6	10.2	Inf
-65	-27	35	Left Cerebrum	Inferior Parietal Lobule	B.A. 40	9.31	Inf
59	14	3	Right Cerebrum	Precentral Gyrus	B.A. 44	9.15	Inf
67	-15	19	Right Cerebrum	Postcentral Gyrus	B.A. 43	8.95	Inf
61	7	20	Right Cerebrum	Inferior Frontal Gyrus	B.A. 44	8.26	7.79
10	-36	66	Right Cerebrum	Paracentral Lobule	B.A. 4	8.71	Inf
0	-7	57	Left Cerebrum	Medial Frontal Gyrus	B.A. 6	8.22	7.76
8	-55	69	Right Cerebrum	Postcentral Gyrus	B.A. 7	7.15	6.85
6	-94	25	Right Cerebrum	Cuneus	B.A. 19	7.44	7.1
6	-98	18	Right Cerebrum	Cuneus	B.A. 18	7.28	6.96
6	-88	34	Right Cerebrum	Cuneus	B.A. 19	7.15	6.84

-36	-61	-22	Left Cerebrum	Fusiform Gyrus	B.A. 37	7.06	6.77
-24	-38	-22	Left Cerebrum	Fusiform Gyrus	B.A. 20	6.21	6.01
-32	-46	-21	Left Cerebrum	Fusiform Gyrus	B.A. 20	5.66	5.5
-50	-11	54	Left Cerebrum	Postcentral Gyrus	B.A. 3	6.81	6.54
-34	-10	63	Left Cerebrum	Precentral Gyrus	B.A. 6	5.95	5.77
44	-5	59	Right Cerebrum	Precentral Gyrus	B.A. 6	6.58	6.34
-16	-59	-9	Left Cerebrum	Lingual Gyrus	B.A. 19	6.08	5.89
46	-63	-22	Right Cerebrum	Fusiform Gyrus	B.A. 37	5.19	5.07
8	65	21	Right Cerebrum	Superior Frontal Gyrus	B.A. 10	5.61	5.46
8	63	13	Right Cerebrum	Medial Frontal Gyrus	B.A. 10	5.61	5.45
42	-30	62	Right Cerebrum	Postcentral Gyrus	B.A. 3	5.59	5.44
36	61	17	Right Cerebrum	Superior Frontal Gyrus	B.A. 10	5.48	5.33
-6	-92	-14	Left Cerebrum	Lingual Gyrus	B.A. 18	5.39	5.25
-10	-103	-2	Left Cerebrum	Cuneus	B.A. 18	5.35	5.21
32	-12	65	Right Cerebrum	Precentral Gyrus	B.A. 6	5.18	5.06
48	-52	50	Right Cerebrum	Inferior Parietal Lobule	B.A. 40	5.18	5.05
32	-65	-19	Right Cerebrum	Fusiform Gyrus	B.A. 19	4.97	4.86
Motor Imagery task – pre-surgery/post-surgery contrast							
16	-4	67	Right Cerebrum	Superior Frontal Gyrus	B.A. 6	6.54	6.24
-14	-8	67	Left Cerebrum	Superior Frontal Gyrus	B.A. 6	6.39	6.1
0	-12	63	Left Cerebrum	Medial Frontal Gyrus	B.A. 6	5.91	5.68
-50	-44	56	Left Cerebrum	Inferior Parietal Lobule	B.A. 40	5.56	5.36
10	-28	66	Right Cerebrum	Paracentral Lobule	B.A. 6	5.54	5.34
51	-74	4	Right Cerebrum	Middle Occipital Gyrus	B.A. 19	5.38	5.2
-48	3	26	Left Cerebrum	Inferior Frontal Gyrus	B.A. 9	5.28	5.11

From a behavioral perspective, the main difference between the pre-surgery and post-surgery session is in the shape and weight of the patient leg. Neither before nor after surgery did the patient report or present at the neurological examination any sensory or motor focal alterations.

Different studies in the literature show that patients with lymphedema report alteration of perceived body image (11,12). Moreover, it is well known that limb conformation affects cortical activations during both motor imagery and active motor tasks (13). Starting from these observations, we believe that the activation changes during the active motor and the motor imagery task could be due to modifications in cortical limb representation.

A further point of interest suggested by this preliminary study is the possibility to better understand sensory-motor restriction in humans. Congenital lymphedema could be a useful disease model to study the effects on cortical organization of a congenital limb mechanical impairment without any neurological involvement.

The main limitations of this pilot study are the lack of a quantitative measurement of patient motor function before and after surgery and that our findings are for now restricted to a single case. Further studies are needed to validate these preliminary results and to understand better their possible clinical relevance and importance.

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TABLE 2
Statistical Contrasts Between Pre-Surgery and Post-Surgery Conditions for the Active Motor and Motor Imagery Tasks

coordinates			Anatomical Localization			voxel	voxel
x	y	z			Broadman Area	T	equivZ
			Active motor task - pre-surgery/post-surgery contrast				
-64	6	14	Left Cerebrum	Precentral Gyrus	B.A. 6	11.42	Inf
-64	2	22	Left Cerebrum	Precentral Gyrus	B.A. 6	10.59	Inf
-62	2	34	Left Cerebrum	Precentral Gyrus	B.A. 6	10.2	Inf
-62	4	26	Left Cerebrum	Precentral Gyrus	B.A. 6	10	Inf
-66	-20	28	Left Cerebrum	Postcentral Gyrus	B.A. 2	6.98	6.7
-66	-10	26	Left Cerebrum	Precentral Gyrus	B.A. 4	6.3	6.09
60	14	4	Right Cerebrum	Precentral Gyrus	B.A. 44	9.15	Inf
68	-16	20	Right Cerebrum	Postcentral Gyrus	B.A. 43	8.95	Inf
62	6	22	Right Cerebrum	Inferior Frontal Gyrus	B.A. 9	8.26	7.79
10	-40	70	Right Cerebrum	Paracentral Lobule	B.A. 4	8.71	Inf
12	-56	72	Right Cerebrum	Postcentral Gyrus	B.A. 7	6.25	6.04
0	-10	62	Left Cerebrum	Medial Frontal Gyrus	B.A. 6	8.22	7.76
6	-10	62	Right Cerebrum	Medial Frontal Gyrus	B.A. 6	7.69	7.32
-50	-12	56	Left Cerebrum	Precentral Gyrus	B.A. 4	6.75	6.49
-46	-14	60	Left Cerebrum	Postcentral Gyrus	B.A. 3	5.85	5.67
44	-8	64	Right Cerebrum	Precentral Gyrus	B.A. 6	6.58	6.34
-34	-14	68	Left Cerebrum	Precentral Gyrus	B.A. 6	5.95	5.77
			Motor Imagery task - pre-surgery/post-surgery contrast				
16	-4	67	Right Cerebrum	Superior Frontal Gyrus	B.A. 6	6.54	6.24
-14	-8	67	Left Cerebrum	Superior Frontal Gyrus	B.A. 6	6.39	6.1
0	-12	63	Left Cerebrum	Medial Frontal Gyrus	B.A. 6	5.91	5.68
-50	-44	56	Left Cerebrum	Inferior Parietal Lobule	B.A. 40	5.56	5.36
10	-28	66	Right Cerebrum	Paracentral Lobule	B.A. 6	5.54	5.34
51	-74	4	Right Cerebrum	Middle Occipital Gyrus	B.A. 19	5.38	5.2
-48	3	26	Left Cerebrum	Inferior Frontal Gyrus	B.A. 9	5.28	5.11

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