Functional relevance of abnormal fMRI activation pattern after unilateral schizencephaly

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Brain plasticity was investigated in a child with a hemiplegia due to unilateral schizencephaly involving the sensorimotor cortex. This focal lesion led to a dramatic functional reorganization of the undamaged hemisphere, as evidenced by the unusual pattern of fMRI activation during paretic finger movements. The functional relevance of the activation in the undamaged motor cortex was supported by the finding that TMS of this area yielded a response in the paretic hand, indicating that it controls both hands. However, this reorganization was not restricted to the primary motor cortex, but also concerned other structures involved in the control of movements, as shown by the activation of contralesional SMA and thalamus. In contrast, the fMRI activation in the damaged sensorimotor cortex during paretic hand movements appears functionally irrelevant. *NeuroReport* 13:1821–1824 © 2002 Lippincott Williams & Wilkins.

Key words: Corticospinal pathways; Functional magnetic resonance imaging; Motor cortex; Transcranial magnetic stimulation

INTRODUCTION

Schizencephaly is a congenital cavitary lesion of the full thickness of the hemispheric wall due either to localised hypoperfusion around the fifth fetal month or to a developmental defect of genetic origin; the cleft is most often bordered by an abnormal polymicrogyric cortex [1–3]. Despite the severity of such a brain malformation, functional imaging studies have shown that a significant activation of the dysplasic cortical areas may still occur during a task performance; this suggests that the dysplasic cortex is functional [4–6] although its actual contribution is impossible to ascertain. Moreover, in some cases, the function normally carried out by the dysplasic areas was shown to be transferred, partially or totally, to the undamaged hemisphere as suggested by its abnormal activation during the task performance [7,8]. However, when the congenital malformation specifically involves the sensorimotor cortex, the functional relevance of fMRI activation in the undamaged hemisphere is questionable because mirror movements, frequently observed in congenital hemiplegia, may cause this activation [8]. The fMRI activation in the undamaged hemisphere may therefore be misleadingly regarded as evidence for brain reorganization whereas it lacks for functional significance.

The goal of the present study was to gain further insight into the functional relevance of cortical area reorganization in a patient with a focal and unilateral congenital malformation of the sensorimotor cortex. The particular question we wanted to address is whether it is possible to ascertain the functional relevance of the dysplasic sensorimotor cortex activation and whether the undamaged hemisphere actually contributes to the control of paretic hand movements. This was performed by combining both fMRI and transcranial magnetic stimulation (TMS) [9].

MATERIALS AND METHODS

The patient was a 9-year-old boy with a right spastic congenital hemiparesis secondary to a left frontal schizencephaly. All experimental procedures were approved by the Ethics Committee of the Université catholique de Louvain and both parents gave written informed consent.

Pregnancy and birth were uneventful. Early left manual preference was observed and walking was acquired at the age of 16 months. Cognitive development was normal and there was no seizure history. At the time of study, the patient showed significant impairment of grip and key pinch strengths and of the digital dexterity of the paretic hand. Strong mirror movements were observed bilaterally. Tactile sensitivity was normal. Although functional scale disclosed a moderate impairment (Brunnstrom score 65/90 [10], Melbourne Assessment score = 71% [11]), a quantitative analysis of the synergy between grip and load forces while

lifting an object with the thumb and index finger showed a severe deficit in scaling adequately fingertip forces, as usually observed in congenital hemiplegic children [12]. The patient had a longer delay between the contact of the thumb and index finger with the object, longer preloading and loading phases, as well as a lower load force rate and a higher grip force.

Anatomical MRI showed a left frontal, closed-lip schizencephalic cleft lined by abnormally thickened cortex with white matter trabecula, suggesting a polymicrogyria. A mild left ventriculomegaly was present (Fig. 1a). The septum pellucidum was absent.

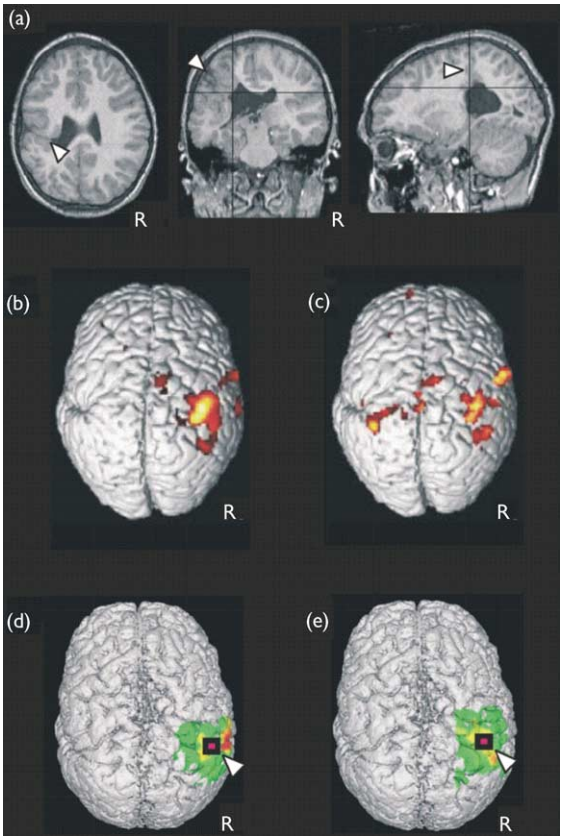

Fig. 1. (**a**) Anatomical MRI shows a left frontal schizencephalic cleft with abnormal gray matter lining the cleft (arrowheads) and a global hemispheric asymmetry with a left ventricular enlargement. (**b**,**c**) fMRI activation maps of sequential finger opposition *vs* rest. Statistical parametric maps are superimposed on surface views (corrected $p < 0.05$, yellow = more significantly activated voxels, red = less activated voxels). (b) Surface rendering of brain regions that were active during non-paretic, left, hand movements: the right sensorimotor, parietal and supplementary motor cortex. (c) Surface rendering of brain regions that were active during paretic, right, hand movements: left dysplasic sensorimotor cortex and parietal cortex, right undamaged sensorimotor and parietal cortex. (**d**,**e**) Cortical IDI representation as evidenced by TMS and co-registered to 3D MRI. Red and green colours indicate zones from which larger and smaller MEPs were evoked, respectively. The centre of gravity of the cortical map is indicate by the magenta square and the arrowhead). (d) Representation of the left (non-paretic) IDI found over the right central sulcus; the centre of gravity was located in the right hand knob. (e) Representation of the right (paretic) IDI found in the right undamaged hemisphere. Both the map area and centre of gravity of the paretic IDI were almost identical to those of the non-paretic muscle. R, Right.

fMRI was performed on a 1.5 Tesla GE-Signa scanner, using a multislice gradient echo-echo planar imaging (GE-EPI) sequence (TR = 4500 ms, TE = 50 ms) with 31 axial slices, 3.8 mm slice thickness (isotropic voxel). The matrix was 64 × 64 and the field of view was 240 mm. Structural 3D MRI was also obtained using a Spoiled Grass (SPGR) sequence (TR = 25 ms, TE = 6 ms, flip angle = 25°, slice thickness = 1.5 mm).

The fMRI paradigm consisted of 14 alternating epochs of self-paced repetitive finger-to-thumb opposition and rest (27 s per epoch, six repetitions, except for the first epoch that lasted for 36 s, eight repetitions). The patient's eyes were closed during acquisition. The first 4.5 s of each fMRI acquisition were discarded because of non-steady condition of magnetisation. The remaining data were realigned to correct for motion (SINC interpolation), using SPM99 (Wellcome Department of Cognitive Neurology). Anatomic MRI was coregistered with fMRI data and matching images were spatially normalised in the stereotaxic coordinate system, with a cubic (2 × 2 × 2 mm) voxel size, and further smoothed with an isotropic Gaussian filter (4 mm FWHM). Statistics were computed with SPM99 for each voxel, with a delayed boxcar function as the reference waveform; the condition effect [activationn-rest] was estimated using the general linear model [13]. Voxels with a level of significance of $p < 0.001$ (uncorrected) were considered as activated.

Transcranial magnetic stimulation of the motor cortex was performed with a Magstim 200 stimulator connected to a figure-of-eight coil. Motor evoked responses (MEPs) were recorded simultaneously from both first dorsal interosseous (1DI). Once the optimal coil position was found, six stimuli were delivered at this site with an intensity of 110% of motor threshold determined according to IFCN committee criteria [14]. Then the coil was displaced by steps of 1 cm and six stimuli were delivered at this new site; this procedure was repeated until no MEPs could be elicited. The 3D coordinates of both the scalp surface and coil position at each stimulation site were acquired using an Isotrack II (Polhemus) and coregistered with the structural 3D-MRI [15]; this allowed us to visualise the 1DI representation on the cortex surface.

RESULTS

Movements of the left non-paretic fingers led to a normal pattern of fMRI activation, namely an activation in the right sensorimotor cortex, right supplementary motor area (SMA), right thalamus and in the left cerebellum; a weak activation was also observed in the left premotor cortex (Fig. 1b; Table 1). In contrast, movements of the right paretic fingers yielded a fMRI activation in both sensorimotor cortices, both cerebellar hemispheres but also in the right (contralesional) SMA and right thalamus (Fig. 1c; Table 1). In the undamaged sensorimotor cortex, the fMRI activation cluster had exactly the same coordinates as that observed during non-paretic finger movements (Table 1). Similarly, the coordinates of the activation locus observed in the right thalamus and SMA were identical irrespective of the hand used to perform the task (Table 1). In the damaged sensorimotor cortex the locus of fMRI activation was found 20 mm deeper than in the undamaged hemisphere.

Table 1. Brain activity during non-paretic and paretic hand movements (sequential finger opposition).

Brain region	Area	Coordinates of foci (mm)			T-scores of foci*	Z-scores of foci**	Volume of activation[a]
		x	*y*	*z*			
Contrast (non-paretic (left) hand movement−rest)							
R. postcentral gyrus	BA3 (SI)	36	−26	46	19.76	> 8	4588
R. precentral gyrus	BA4 (MI)	42	−16	54	13.63	> 8	(same cluster)
R. central sulcus		38	−26	64	12.93	> 8	(same cluster)
R. superior frontal gyrus	BA6 (SMA)	12	2	48	12.06	> 8	761
L. cerebellar vermis		−8	−48	−8	11.73	> 8	641
R. thalamus		14	−12	12	7.71	6.46	160
L. superior frontal gyrus	BA6 (PM)	−14	16	46	6.66	5.78	166
Contrast (paretic (right) hand movement−rest)							
L. postcentral gyrus[b]	BA3 (SI)	−30	−36	36	13.63	>8	3329
L. parietal cortex	BA40 (LPI)	−42	−38	50	11.71	> 8	(same cluster)
L. precentral gyrus[b]	BA4 (MI)	−24	−26	44	11.47	> 8	(same cluster)
R. superior frontal gyrus	BA6 (SMA)	12	2	48	9.68	7.57	(same cluster)
R. precentral gyrus	BA6 (PM)	58	−4	42	11.31	> 8	1279
R. postcentral gyrus	BA3 (SI)	36	−32	54	10.86	> 8	2511
R. central sulcus		38	−22	48	10.58	> 8	(same cluster)
R. precentral gyrus	BA4 (MI)	42	−18	54	10.18	7.80	(same cluster)
R. cerebellar hemisphere		12	−46	−16	8.12	6.70	290
R. cingulate gyrus	BA32-24	8	16	36	7.53	6.35	229
L. cerebellar hemisphere		−22	−62	−18	7.42	6.28	457
R. superior temporal gyrus	BA22	50	−8	2	7.18	6.12	109
R. cingulate gyrus	BA32	0	38	28	6.56†	5.71	104
L. superior frontal gyrus	BA10	−12	66	8	6.39†	5.59	384
L. middle frontal gyrus	BA8	−26	34	38	6.25†	5.50	218
R. thalamus		16	−10	12	5.82††	5.19	368

L., left; R., right; BA, Brodmann area; SI, primary sensory area; MI, primary motor area; SMA, supplementary motor area; LPI, inferior parietal lobule; PM, premotor cortex.
*Significant peaks of fMRI signals (corrected *p* values at the cluster level < 0.001, extent threshold = 100 voxels).
**Significant peaks of fMRI signals (corrected *p* values at voxel level 0.001, except †$p = 0.005$, ††$p = 0.023$).
[a]Number of suprathreshold ($Z = 5.19$) voxels of the clusters.
[b]Abnormal polymicrogyric cortex lining the schizencephalic cleft.

Despite the fMRI activation observed in the damaged sensorimotor cortex during paretic finger movements, TMS applied over this area failed to elicit MEPs in the paretic hand, even at maximal stimulator output. In contrast, TMS applied over the undamaged motor cortex evoked short-latency MEPs in the 1DI of both hands. Both the latency and motor threshold of the left and right 1DI responses were statistically indistinguishable and the centre of gravity of both 1DI maps were located in the hand knob of the right precentral gyrus (Fig. 1d,e).

DISCUSSION

The present study shows that a focal congenital malformation of the sensorimotor areas may induce a profound functional reorganization of the undamaged hemisphere. This is evidenced by the significant fMRI activation of the undamaged motor cortex during paretic finger movements and further supported by the finding that TMS of the undamaged motor cortex yielded responses in the paretic hand. Those observations indicate that the undamaged motor cortex controls movements of both hands but, additionally, we found that the reorganization of the undamaged hemisphere was not restricted to the motor cortex. The significant activation in the contralesional SMA and contralesional thalamus during paretic hand movements suggests that this reorganization concerned a larger network of structures involved in the control of voluntary movements. Finally, the present results give little support to the functional relevance of the fMRI activation observed in the damaged sensorimotor cortex during paretic hand movements.

In congenital hemiplegic patients, fMRI activation of the undamaged sensorimotor cortex during paretic hand movements is usually regarded as evidence for functional reorganisation of the cortical areas involved in the control of hand movements [8,16]. However, since mirror movements are frequently observed in the non-paretic hand [3], fMRI data on their own do not allow us to discard that the activation of the undamaged sensorimotor cortex is not related to mirror movements [8]. In the present study, the finding that TMS of the undamaged motor cortex elicited simultaneous MEPs in both hands permitted to rule out this hypothesis and confirmed that the undamaged motor cortex is actually involved in the control of paretic hand movements. Indeed, simultaneous bilateral MEPs are usually regarded as evidence for bilaterally branched corticospinal projections to the spinal cord [17], indicating that, in this patient, early sensorimotor cortex lesion has induced a profound reorganization of the corticospinal projections, in accordance with previous studies [18,19]. In addition, the present results point out

that the functional reorganisation of the undamaged hemisphere was not restricted to the primary motor cortex [20] but also concerned the non-primary motor areas and somatosensory system [16,21], as shown by the activation of the contralesional SMA and thalamus during paretic finger movements.

Along this line, if the contralesional hemisphere is responsible for controlling paretic hand movements, it is sensible to question the functional significance of the fMRI activation found in the dysplasic sensorimotor cortex during paretic finger movements. Although this activation may be regarded a priori as evidence that dysplasic cortical areas have preserved a certain functional capacity, in agreement with previous studies [4–6,22], the absence of responses in the paretic hand muscles to TMS of the dysplasic motor cortex challenged this interpretation. The key question is therefore whether this absence of responses to TMS indicates undoubtedly a lack of corticospinal projections or simply reveals a failure either to disclose weak corticospinal connections or to activate corticospinal cells more deeply located in the schizencephalic cleft than in the undamaged motor cortex. For threshold finger movements, the depth of TMS has been estimated at about 20 mm [23] and the maximal output stimulation we used should have penetrated deeply enough to recruit corticospinal cells in the dysplasic motor cortex. Alternatively, it is possible that the descending volleys evoked by TMS were too small, or too temporally dispersed, to bring motoneurones to fire. Although we cannot rule out definitely this objection, this seems unlikely since this patient had upper limb spasticity and his motoneurones should be particularly responsive to descending corticospinal volleys; the finding that its motoneurones were easily recruited by TMS of the undamaged motor cortex further supports this view. In conclusion, it is therefore sensible to assume that, in this patient, the absence of responses to TMS of the damaged motor cortex revealed a lack of corticospinal projections from this hemisphere, as already described in severe congenital hemiplegia [16,18] and this suggests that fMRI activation of the dysplasic motor cortex does not relate to the execution of paretic hand movements. However, it could be hypothesised that the residual fMRI activation in the dysplasic motor cortex reveals its contribution, possibly via the transcallosal connections, to the programming of paretic finger movements. Alternatively, this fMRI activation could be an epiphenomenon resulting from a lack of transcortical inhibition from the undamaged motor cortex [24] or from an abnormal metabolism in early disconnected or injured cortical areas [25].

CONCLUSION

The present study provides further evidence that, in humans with early brain lesion, the corticospinal system has great possibilities of reorganization, probably because of its protracted development. In addition, our results show that a focal malformation of the sensorimotor areas may also yield functional reorganization of a vast network of structures including the non-primary motor areas and the thalamo-cortical connections.

Interestingly, despite the rather dramatic functional reorganization of the cortical network that controls voluntary movements, the hand function of this patient was rather satisfactory; only very dextrous movements involving an accurate control of precision grip between the thumb and the index finger were severely impaired [12], unveiling the unparalleled contribution of the crossed corticospinal pathway in skilled finger movements.

Finally, the present study shows that, although fMRI activation may be present in the dysplasic cortex, such an observation on its own cannot be used to infer the actual contribution of the damaged hemisphere in the control of paretic hand movements. The present study further emphasises the advantage of using different approaches to address the issue of functional brain reorganization in the particular context of early foetal malformations.

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