Neurocase (2006) **12**, 232–235

ISSN: 1355-4795 print / 1465–3656 online
DOI: 10.1080/13554790600878879

Psychology Press
Taylor & Francis Group

Dysfunction of a Structurally Normal Motor Pathway in a Brain Injury Patient as Revealed by Multimodal Integrated Techniques

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We report on a patient with left hemiparesis and peripersonal neglect after post-traumatic left frontal hemorrhage, who underwent fMRI, TMS and TCD to identify the functional abnormalities that account for his neurological symptoms, in the absence of any detectable lesion affecting right motor areas.

Introduction

Several non-invasive techniques are available to test the functionality of the motor system. Functional Magnetic Resonance Imaging (fMRI) and Transcranial Magnetic Stimulation (TMS) have been widely employed to study both the physiology and functional topography of the motor system as well as the rearrangement of the sensorimotor areas after brain damage (Hallett, 2000; Ward and Frackowiak, 2004) Moreover, altered hemodynamics, possibly influencing motor plasticity in ischaemic patients, might be revealed by Transcranial Doppler (TCD) examination (Rossini *et al*., 2004).

We report on a patient with left hemiparesis and peripersonal neglect after post-traumatic left frontal hemorrhage, who underwent fMRI, TMS and TCD in order to identify the functional abnormalities that account for his neurological symptoms, in the absence of any detectable lesion affecting right motor areas. In particular, this multimodal approach aimed at assessing whether right motor area excitability was impaired as a consequence of the traumatic brain injury.

Quantitative fMRI, TMS and TCD showed reduced activation in the right motor area, reduced motor cortex excitability of the right compared to left hemisphere and altered vasomotor reactivity on the right side, respectively.

These findings suggest that this combined methodological approach could reveal an impairment of the functionality of the motor system in post-traumatic patients, even in the absence of clearly detectable lesions.

Received 21 January 2006; accepted 19 June 2006.

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Case Report

A 47-year-old man was hit by a car, suffering closed head trauma and politrauma. Comatose, he was admitted to the Emergency Department (Glasgow Coma Scale:4) (Teasdale, 1974).

Hemorrhagic lesions in the left frontal lobe have been disclosed by cerebral CT scan. Submitted to pharmacological sedation, he went into a coma that lasted 15 days. At awakening, he showed left hemiplegia and psychomotor agitation. Two MRIs (2nd and 25th day post-injury) revealed focal abnormalities in frontal and temporal left areas as well as in the corpus callosum.

He was admitted to the Post-Coma Unit of our Institute, one month after the trauma. He was alert but amnesic, confused and agitated (Level of Cognitive Functioning -LCF 4) (Hagen *et al*., 1972) with frequent confabulations and perseverative behavior. He showed left hemiparesis with left facial weakness, dysphonia and slight left personal and peripersonal neglect. He was unable to walk.

One month later, neuropsychological assessment revealed: apathy, post-traumatic amnesia and slight personal neglect.

Three months after trauma his motor deficits improved: he was able to use his left hand in daily life and to walk autonomously but he still showed mild left hemiparesis, dysmetria and gait ataxia. Moreover, upper limb motor impairment evaluated by the Motricity Index was sixty (Demeurisse *et al*., 1980).

In that period, clinical MRI, conventional and quantitative fMRI, TMS and TCD were carried out.

Both MRI and fMRI were performed at 1.5T (Vision Magnetom, Siemens Medical Systems, Erlangen, Germany). The clinical protocol consisted of Fluid Attenuated Inversion Recovery (FLAIR), T1-, T2-, and T2* -weighted MRI. Morphological evaluation revealed the presence of T2*-hypointense lesions located in the frontal (primary motor and premotor areas) and temporo-mesial cortices and in the corpus callosum of the left hemisphere, indicating focal

hemosiderin deposits in the chronic stage and excluding other possibly related morphologic abnormalities, such as focal calcifications or small vascular malformations (Figure 1). Two runs of functional MRI (68 volumes each, multi-echo EPI, resolution: 3 × 3 × 4 mm, 22 slices, echotimes, TE: 23, 64, 105, and 145 ms, repetition time, TR = 4 s) were carried out while the patient performed a motor task key-press with index fingers of both hands, in synchrony with an external visual cue, indicating which hand to use. Image analysis was performed in SPM2 and included motion correction, unwarping (Andersson *et al*., 2001), generation of quantitative T_2* maps and proton-density images (Hagberg *et al*., 2002), spatial smoothing (6mm), brain masking and statistical analysis of conventional and quantitative fMRI data ($p < 0.05$, corrected for multiple comparisons by the Family Wise Error procedure). T2* time courses were extracted from the activated areas and *post-hoc* statistical comparisons were performed.

Psychophysics measurements performed during this simple motor task indicated a similar performance between the right and left hand. Both conventional and quantitative fMRI showed brain activation in the left primary motor cortex for the right, unaffected hand (Figure 1). Conversely, only quantitative fMRI was able to reveal brain activations associated

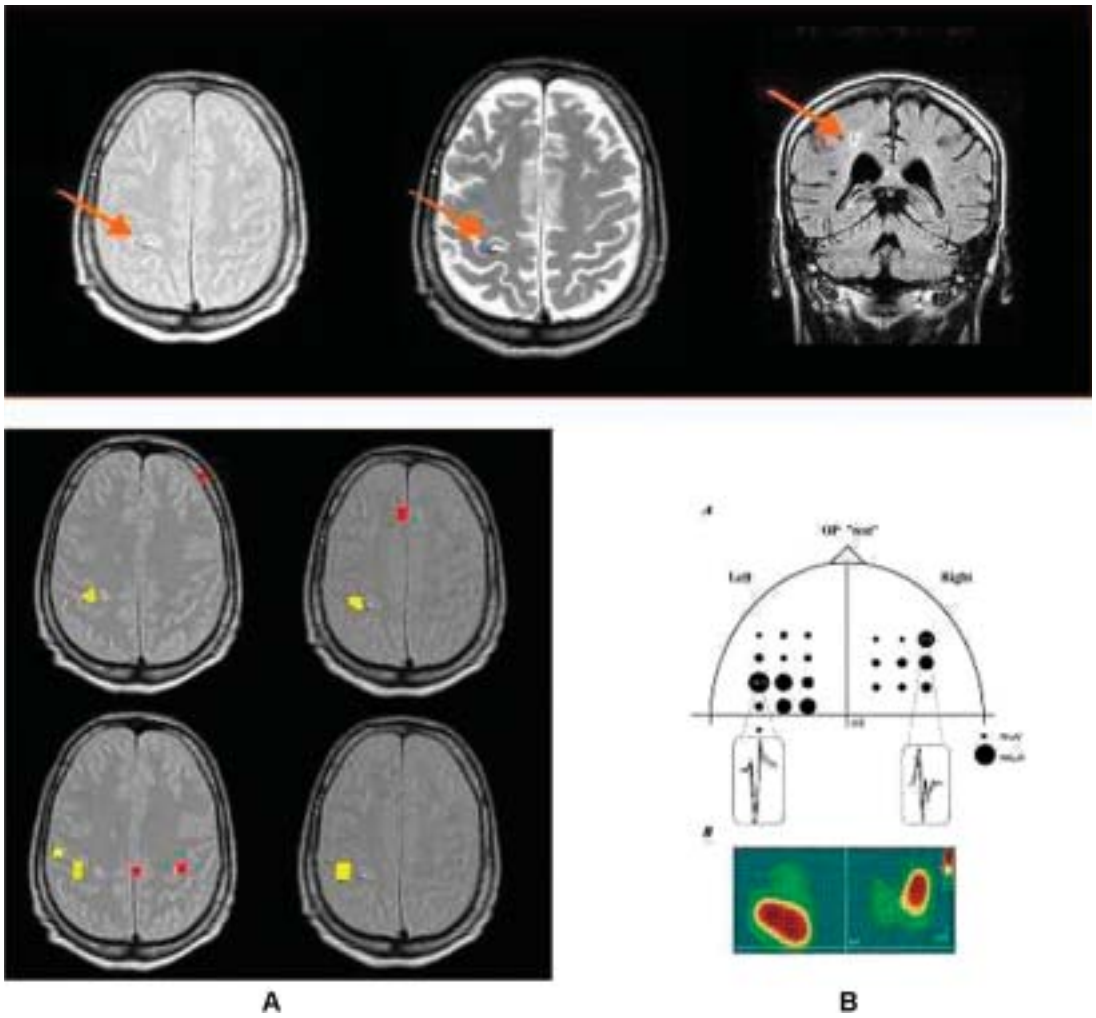

Fig. 1. Upper Row: Clinical MRI. From left to right: proton density, T2-weighted and FLAIR images. The lesion in the left hemisphere is indicated by the red arrow. Lower row (on the right) Activation patterns obtained by conventional fMRI (upper row) and quantitative fMRI (lower row). The clinically asymptomatic right hand resulted in significant signal changes in the left primary motor area (yellow) in both conventional and quantitative fMRI. In contrast, conventional fMRI did not reveal any activation in motor areas for the affected left hand (activated pixels in superior frontal gyrus and outside brain) while quantitative fMRI yielded significant activations not only in the primary but also the supplementary motor areas (red). Lower row (on the left) **A** Schematic head of the patient showing the scalp positions from which MEPs of the OP muscles are elicited. The circle's dimension is proportional to the real MEPs amplitude (from 50 to 500 micronV) obtained from each site. The full-size circle (H-S) represents the hot-spot of the maps and the insets below show the original MEPs obtained from the hot-spot of both hemispheres. **B** Two-dimensional flattened reconstruction of the OP muscle cortical maps in both hemispheres of patient. The color code palette ranges from dark green (0 μV) to dark red (500 μV). The scale bar used is 1 cm for both *x* and *y* axes.

with movement of the left affected side in motor areas, in line with previous results demonstrating an improved sensitivity of quantitative fMRI (Hagberg *et al*., 2003). In particular, fewer voxels (1 voxel) were detected in the right, primary motor area serving the affected hand, compared to the left M1 (8 voxels). In addition, fMRI activation involved more motor areas, including the supplementary motor area, probably in order to achieve a normal motor performance with the affected hand (Figure 1). Finally, the average increase in T2* values due to activation was significantly less ($p < 0.01$) in the right M1 (2.0 ± 2.2 ms) than in the left (4.3 ± 2.2 ms) hemisphere and the resting T2* values were also noticeably reduced for the affected hand. Although the observed T2* values were not significantly different from values found in healthy volunteers (n = 10), interhemispheric differences in T2* changes exceeding 100% were unexpected.

MEPs were recorded from the relaxed OP muscles contra- and ipsilateral to the stimulated hemisphere with a pair of 12 mm diameter surface Ag-AgCl electrodes taped in a belly-tendon montage. Motor maps were gathered through a "figure-of-eight" coil connected with a magnetic stimulator (MagStim Co, Withland, UK). A grid of 49 positions, spaced 1.5 cm on both the medio-lateral and antero-posterior axis, was tested on each hemisphere covering the precentral area. The center of the grid was positioned over the "hot spot" site defined as the site whose stimulation elicited MEPs of the highest amplitude and shortest latency.The intensity of TMS was 10% above the excitability threshold for MEPs elicitation, identified according to standardised criteria (Rossini *et al*., 1994). Motor maps "area" (number of scalp positions from which MEPs were elicited) and motor maps "volume" (sum of the averaged MEPs amplitude from each excitable scalp positions) were measured. When possible, statistical comparison was performed (Student's *t*-test).

During the mapping session, no ipsi-MEPs were recorded following TMS of both right (RH) and left (LH) hemispheres. Excitability threshold was higher in the RH (82%) compared to LH (62%). The "hot-spot"-MEP's latencies and amplitudes were bilaterally within normal limits and no interhemispheric differences were observed. However, a clear asymmetry of the OP muscle map area and volume was demonstrated between the two hemispheres due to a reduced cortical representation in the RH compared to the LH (Figure 1). The motor maps topography of the two hemispheres, as measured by the "hot-spot" localization, was symmetrical on the medio-lateral axis, whereas a consistent rostral shift was observed on the antero-posterior axis in the RH compared to LH (Figure 1).

Mean flow velocity (MFV) of the right and the left middle cerebral artery (MCA) was continuously monitored by means of a MultiDop X/TCD transcranial Doppler instrument (DWL Elektroniske Systeme GmbH, Germany). Two dual 2-MHz transducers fitted on a headband and placed on the temporal bone window were used to obtain a bilateral continuous measurement. This unit allows for continuous-wave Doppler recording of the intracranial artery with on-line calculation of MFV in centimeters per second. By activating the record function, it is possible to save the Doppler spectra during the entire period of study. Vascular reactivity to hypercapnia was studied by calculating the breath-holding index (BHI) (Markus and Harrison, 1992). This index was obtained by dividing the percentage increase in MFV occurring during breath-holding by the time (seconds) during which the subjects hold their breath after a normal inspiration. Mean flow velocity at rest was obtained by the continuous recording of a 2-minute period of normal room air breathing. After a breath-holding period of 30 s, the MFV over 4-s interval was recorded. The efficacy of breath-holding was checked by means of respiratory activity monitoring (Normocap-oxy, Datex, Italy). The BHI experiment was repeated three times separated by 10-min intervals and then the data were averaged. The patient showed a clear by impaired vasoreactivity on the right side (BHI: 0,50) respect to the left side (BHI:1,30). Extracranial and transcranial Doppler showed no sign of carotid or intracranial stenosis.

The last neuropsycological observation, 4 months after trauma and cognitive therapy, demonstrated a slight memory deficit and persistent apathy.

Discussion

The most notable clinical feature of this patient was the development of left hemiparesis associated with a focal hemorrhage in the left primary motor and premotor cortices. The absence of any detectable morphological lesion in the right cortical motor areas and in the pyramidal tracts was demonstrated by several MRI examinations.

Clinical case reports have demonstrated the existence of uncrossed pyramidal tracts in exceptional patients with hemiparesis homolateral to cerebral lesions (Terakawa *et al*., 2000) However, in our case, magnetic stimulation of the primary motor area evoked contralateral responses from the hand muscles and failed to detect any motor responses ipsilaterally to the stimulated hemisphere, suggesting that the pyramidal tract was normally crossed.

The integration of four biomedical methods allowed a complementary analysis of several functional and anatomical aspects. Although MRI indicated a lesion in the left hemisphere, other techniques evaluating the functionality of the motor system demonstrated that this lesion was functionally silent. In contrast, careful examination of the unlesioned right hemisphere showed both neuronal and vascular deficits. TMS mapping demonstrated a lower excitability of the cortical representation of the affected hand and quantitative fMRI disclosed less activated voxels for the symptomatic than for the asymptomatic hand. All the techniques performed demonstrated unexpected interhemispheric differences in comparison to healthy controls and in particular, for TMS mapping, this asymmetry could not be due to the differences of the hand motor cortical output, since they have been shown to be minimal between the right and left hemisphere

of healthy subjects (for details of the normative database see Cicinelli P *et al*., 1997).

These results extended TCD findings. In particular, while TCD demonstrated a generalized decreased vascular reactivity of the right hemisphere, the reduced change in T2* values between active and resting state in M1 showed how the globally reduced vascular reactivity was also expressed by a local decreased efficacy of the hemodynamic system. Both right primary and supplementary motor areas were activated during left finger movements, while only M1 was active for the unaffected hand. The activation of a more widespread brain network in the right hemisphere was probably necessary to maintain a normal performance, consistent with the clinical features. However, we cannot exclude that this result was due to a different amount of attention and programming devoted to the control of hands.

Rossini *et al*. (2004) performing a similar integrated approach in nine patients affected with a cerebrovascular disease, showed a lack of fMRI activation strongly related to altered vasomotor reactivity as measured by TCD. The absence of the BOLD signal was hypothesized to stem from neurovascular impairment. Krakauer *et al*. (2004) suggested that an atypical pattern of functional activity was induced by the physiologically unfavorable environment of low blood flow on the side of carotid occlusion in six patients, even in the absence of any structural brain injury or neurological deficit.

In our post-traumatic patient, abnormal findings in the right motor area could be related to a similar alteration of cerebral hemodinamics secondary to brain injury, not diffuse as in cerebrovascular diseases but confined within one hemisphere. Cerebral hemodynamic abnormalities such as hypoperfusion and loss of autoregulation are important pathophysiological elements in stroke and traumatic brain injury (TBI), but the influence of impaired hemodynamics on clinical brain function after injury is largely unknown (Marshall, 2004). The "neurovascular coupling", a dynamic interaction between the neurons and blood vessels, generally becomes disordered after head trauma.

The pathophysiology might include a direct effect on the myogenic tone of cerebral arteries (Cipolla and Curry, 2002), and a post-injury imbalance of circulating and endothelium-derived vasoconstrictive and vasodilatory substances, including inflammatory factors (Golding, 2002).

Some authors attempt to correlate anatomical MRI abnormalities with clinical outcome in post-traumatic patients (Pierallini *et al*., 2000). Our study suggested that in some brain injury patients integrated investigations could help in identifying functional abnormalities underlying neurological features, even if not clearly related to morphological lesions. These functional data should be taken into account to better explain the relationship between damaged cerebral areas, clinical features and recovery from neurological impairments in traumatic brain injury patients. Finally, new advanced MRI techniques, such as relaxometry, diffusion weight imaging (DWI) and diffusion tensor imaging (DTI), spectroscopy (MRS) could allow more accurate and precise evaluation of lesions, detection of structural and metabolic alterations in white or grey matter, apparently normal, and their localization toward nerve pathways.

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