

FUNCTIONAL MAGNETIC RESONANCE IMAGING AS A TOOL FOR INVESTIGATING HUMAN CORTICAL MOTOR FUNCTION

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INTRODUCTION

The recent development of noninvasive functional magnetic resonance imaging (fMRI) techniques, sensitive to the local changes of blood flow, blood volume, and blood oxygenation which accompany neuronal activation, has provided a new powerful tool for the study of human brain function (12, 58, 70). fMRI does not require radioactive tracers, thus allowing repeated investigations in the same subject. Moreover, it is characterized by a better spatial and temporal resolution than conventional positron emission tomography (PET) (12, 81), and it is therefore well suited to analyze the spatio-temporal dynamics of brain activation.

I. Basic principles of functional magnetic resonance imaging

Imaging of brain function by fMRI is based on the detection of changes in the intensity of the proton signal of tissue water, that result from local hemodynamics and metabolic changes (57, 69, 70, 95). It is well established that local increases in the activity of neuronal assemblies induce regional variations of blood flow and blood volume, glucose utilization, and oxygen consumption. However, the percentage changes in oxygen consumption and blood volume are much lower than those in blood flow (24, 25, 81). As a result, there occurs a paradoxical decrease of the oxygen extraction fraction, and therefore a decrease in the regional concentration of deoxyhemoglobin. This substance is more paramagnetic than oxyhemoglobin (which itself has almost exactly the same magnetic susceptibility as tissue), and can therefore be seen as an endogenous contrast agent. Decreases in deoxyhemoglobin levels cause indeed increases in the relaxation time constant, T_2^* , of tissue in the vicinity of blood vessels. The resulting signal changes are the base of the so called BOLD (blood-oxygenation-level-dependent) contrast (36, 69, 96). The BOLD signal increases with field strength and can in principle be affected by changes in blood arterial oxygenation, blood volume, blood flow, hematocrit, tissue oxygen uptake and possibly blood velocity: detailed modeling and experimental investigation are still in progress (10, 17, 55, 95). Other fMRI techniques, based on the detection

of changes in the relaxation time constant T_1 , are specifically flow-sensitive and may be used to calculate relative or absolute changes of blood flow in response to sensory, motor or cognitive tasks (22, 53, 59). Readers are referred to the specific literature for detailed review of the physics and physiological basis and of the temporal and spatial characteristics of fMRI (3, 4, 13, 52, 54, 57, 84, 95). Images obtained by this technique may be statistically analyzed by different approaches (57, 74), e.g. using the Student's *t* test or cross-correlation analysis (2, 56), Fourier analysis (28), general linear model and the theory of Gaussian fields (27).

Different aspects of the functional organization of motor areas have been studied using fMRI (1, 61), such as the relationships between parametric and other aspects of movement (rate, force, external or internal trigger) and the intensity or the spatial extent of the activation (21, 41, 76, 90, 98, 101), somatotopy (78, 89), hemispheric specialization (6, 16, 50), learning and training effects (38, 46, 47), plasticity after damage (67) and their involvement in motor imagery (51, 63, 73, 85). The present work, which is not intended to be a comprehensive review, will briefly touch upon some of these issues, focussing on studies on the primary motor cortex.

II. Functional aspects of motor cortex activation during contralateral arm movements

The intensity of BOLD signal changes in the primary motor cortex during motor performance varies in individual subjects and is related to field strength, to the adopted fMRI sequence and acquisition parameters, and to the characteristics of movement. Percentage changes from baseline in activated neural clusters may reach 10% in high-resolution studies using fast-low-angle-shot (FLASH: 37) gradient-echo imaging techniques at 1.5 Tesla (T), even when large vessels are not considered (65, 73, 102), whereas it is usually less (1-5%) using echo-planar imaging (EPI: 58) or 3D fMRI scans based on principles of echo shifting with a train of observations (PRESTO: 75, 97). These differences may be related at least in part to the so called "partial volume" effects when the spatial resolution worsens. Higher signal changes (up to 75%) are detected by fMRI techniques sensitive to parenchymal cerebral blood flow (e.g., 89).

Within subjects, the intensity of fMRI signal changes and/or the number of activated voxels in the contralateral primary motor cortex covaries with movement rates during repeated finger flexion-extensions or sequential finger tapping (41, 76, 88, 90, 101). These findings may be ascribed to factors directly related to timing, such as the activation of additional neurons necessary for increased output to target motoneurons when movements become faster, although the recruitment of additional muscles acting on nearby joints might also contribute. Both in right-handed and left-handed subjects, use of the dominant hand is associated with greater activation compared with the non-dominant hand (as expressed by the volume of activated tissue) in the contralateral primary motor cortex (16). However, complexity of movements does not appear to affect significantly the spatial extent or the intensity of activation in the primary motor cortex of the dominant hemisphere (98, 101).

As expected, the pattern of functional activity in the precentral gyrus follows a

gross topographic representation: toe movements are associated with fMRI signal changes at the interhemispheric fissure or in the adjacent dorsolateral cortex, whereas finger movements induce the most robust signal changes in a more lateral location, over the convexity of the cortex (78). In general, the area of activation in the motor cortex during hand movements appears to be rather small compared with the region from which movements can be elicited by electrical stimulation (49, 72). Moreover, Rao et al. (78) noted an overlap between the functional changes induced by elbow and finger movements. This issue has been investigated in more detail by Sanes et al. (89), using a flow-sensitive fMRI technique. Finger and wrist movements activated overlapping volumes in the posterior half of the contralateral precentral gyrus, in a middle area corresponding to the "classical" hand region of the primary motor cortex (14, 34, 35, 72). Multiple sites of activation occurred for all movements, suggesting the involvement of coordinated and distributed networks of precentral neurons during the execution of different hand movements, rather than a discrete somatotopic representation of single segments. This is in line with the hypothesis advanced by J.H. Jackson (40) that the motor cortex represents movements rather than body parts.

A further point concerns the contribution of sensory (tactile or proprioceptive) input to the observed signal changes during motor tasks. Activation in two adjacent gyri, presumably corresponding to the contralateral primary sensory and motor cortices, was found during continuous tactile stimulation of the palm in approximately two-thirds of subjects using gradient-echo EPI (105), suggesting that exteroceptive information may induce significant fMRI signal changes in MI. However, similar fMRI activation maps were obtained in finger tapping tasks, either when subjects were required to touch fingertips with the thumb or to perform similar opposition movements without touching fingers (42).

Although the hemodynamic response lags behind neural changes (2, 5, 28, 58), recent studies using single-trial fMRI have demonstrated sequential activation of the supplementary motor area and of the primary motor cortex during self-paced finger movements (103), and differential changes of activity during movement preparation and execution in the primary motor cortex and in the supplementary and lateral premotor cortex (80). These findings are of great relevance, inasmuch as they show that fMRI may give information on the temporal aspects of the activation of functionally connected cortical networks.

III. Comparison with data acquired using positron emission tomography

In studies in which the same subjects were tested during finger movement tasks using either positron emission tomography (PET) scans employing labeled water ($H_2^{15}O$) to investigate regional cerebral blood flow (rCBF), or BOLD-sensitive or flow-sensitive fMRI sequences, the locations of the activated clusters detected by the two methods in the primary sensorimotor cortex contralateral to the moving hand were closely related (21, 75, 88). Since the distribution of $H_2^{15}O$ reflects rCBF (23, 26), these results show that the BOLD signal changes detected by fMRI techniques agree highly with (and in fact, are directly or indirectly dependent on) local blood flow changes.

In one investigation (21), healthy volunteers were studied by $H_2^{15}O$ PET and by the 2D FLASH fMRI technique, while repeatedly pressing a key with the right index finger at the same frequency of 1 Hz but at different forces, ranging approximately from 5 to 60% of the individual maximal voluntary contraction. Both PET and fMRI revealed activation of the contralateral primary motor cortex and posterior supplementary motor area in all the investigated subjects. The relationship between rCBF, or fMRI signal, and force fitted a logarithmic function. Although the maximum increase was estimated to be approximately 14% for rCBF and 5% for the fMRI signal, the ratio between relative rCBF and relative fMRI signal increases was constant for all force levels. In another study (88), the effects of repetition rate of a simple movement on the magnitude of the response in the contralateral primary sensorimotor cortex was studied by PET and a flow-sensitive fMRI technique. fMRI proved to be more sensitive in separately identifying different components of the increasing neural activation to higher movement speeds, namely the spatial extent of the recruited area (which increased up to 2 Hz and then declined) and the percent change in signal intensity within the activated voxels (which increased linearly from 1 to 4 Hz).

IV. Activation of the primary motor cortex during ipsilateral arm movements

Activation of the ipsilateral sensorimotor cortex during proximal arm or finger movements has been detected in healthy volunteers by different research groups using PET (14, 48, 79, 87, 91).

In fMRI investigations performed on a 4 T system in right-handed volunteers, it was found that both peak intensity changes and the surface area of activation were less in the right precentral gyrus during ipsilateral than contralateral finger tapping (49, 50). In two studies from the same group, the mean contralateral/ipsilateral ratios between the extent of the activated areas were 20:1 and 36.8:1, respectively. Mean percentage signal increases over baseline values were approximately 9% during the contralateral and 5% during the ipsilateral movement. In an ambidextrous subject, the area of activation during ipsilateral movements was only 2.3 times smaller than during contralateral ones. The intensity of fMRI signal changes was higher when subjects moved the fingers of both hands, but the area of activation was similar during the bilateral and the contralateral task (49). By contrast, no significant difference was found in right-handers between the spatial extent of the activation of the left primary motor cortex during contralateral vs. ipsilateral movements (ratio = 1.3). The same pattern of hemispheric differences, although less pronounced, was present in left-handers (50). A negative correlation was found in another study from the same group between the degree of handedness and the extent of activation in the primary motor cortex ipsilateral to the dominant hand (16).

Several fMRI studies performed at lower field strength (1.5 T) have also found activation of a region corresponding to the primary sensorimotor cortex during ipsilateral hand or wrist movements in right-handers, often only in some subjects (e.g., 7, 8, 9, 77). In these studies, a clear difference in the extent of the activated area in the left (dominant) hemisphere during left or right motor activity was

usually found (101). In patients with unwanted mirror movements, a significant increase in the mean volume of activation around the central sulcus was found in the hemisphere ipsilateral to the intentionally moved hand relative to healthy controls (62).

Altogether, these results suggest an hemispheric specialization of motor areas concerning the control of ipsilateral movements, and they confirm and extend previous neurophysiological findings showing that a small proportion (~8%) of neurons in the ipsilateral precentral gyrus display activity related to simple motor tasks (93), and that lesions of area 4 induce a detectable although transient decrease in grip strength on the ipsilateral side (32). Clinically, a decrease in muscle strength and impairment of complex movements on the ipsilateral side have been documented in patients with hemiplegia (15, 45). It is known that 10-15% of fibers in the lateral cortical spinal tracts are uncrossed in human and nonhuman primates (68, 104). It is uncertain, however, whether the observed ipsilateral fMRI signal changes may reflect activation of corticospinal neurons projecting ipsilaterally, since only a small amplitude response of ipsilateral hand muscles can be detected following transcranial magnetic stimulation, and this activation appears to be present only during voluntary muscle contraction (7, 66, 100). It has been hypothesized that the ipsilateral activation might rather reflect the presence of networks involved in bilateral motor planning, connected through rapid callosal pathways (39). The major role of the dominant hemisphere at this regard is supported by a greater extent of the activation during bimanual finger movements in the left hemisphere in right-handers (41), and by studies on changes in motor behavior consequent to callosotomy (29, 99) or transcranial magnetic stimulation (11).

To advance knowledge on this issue, it is interesting to determine whether neural populations exist in the human primary motor cortex which are involved uniquely during ipsilateral hand movements, and whether cortical networks activated during movements of either hand, or only of the contralateral hand, are spatially segregated within the precentral gyrus and adjacent lateral premotor cortex. This issue has been investigated by our group using echo-planar fMRI techniques on a 1.5 T clinical scanner (6). Healthy volunteers were asked to perform periods of sequential finger tapping of the right dominant hand or of the left hand, alternated with rest. The experimental design allowed us to test directly whether the same brain regions were activated during movements of either hand. The results provided evidence for two pixel populations in the left precentral gyrus (dominant hemisphere), the one showing activation exclusively during contralateral finger movements, and the other involved both during left and right hand movement. The "bilateral" population was less prominent in the right precentral gyrus. A spatial segregation appeared to exist, inasmuch as the bilateral representation tended to cluster more anteriorly in the rostral half of the precentral gyrus, a region likely corresponding to area 6, whereas the population activated during contralateral movements predominated in the posterior part of the gyrus (area 4). No pixels showing exclusively ipsilateral representation were found.

This study confirms a preferential involvement of the dominant hemisphere in programming bilateral movements. *Furthermore, it demonstrates that populations*

with different characteristics may be identified using fMRI within the same anatomically defined cortical regions. Thus, the functional organization of human cortical circuits may now be investigated at a macrocolumnar level (12).

V. fMRI signal increases in the primary motor cortex during motor imagery.

The neural substrates underlying mental representations of motor acts (motor imagery) have been extensively investigated over the past two decades, using a variety of brain mapping techniques. Several single-photon emission tomography (SPET) or PET studies demonstrated the activation of different motor-related regions, such as the supplementary motor area, lateral frontal premotor areas, and cerebellum, but they did not provide evidence for increased activity in the primary sensorimotor cortex during imagery of different kinds of movements (19, 20, 33, 71, 82). However, activated foci in or around the primary motor area have been described in a PET study (60) during oculomotor imagery and in PET (92) and fMRI (51, 63, 86) studies during mental representation of upper extremity movements, at least in some subjects. However, no quantitative assessment of the relative contribution of pre- and post-central areas was done.

In a recent study (73), we have investigated by high-resolution fMRI, using a clinical 1.5 T system, whether perirolandic areas show increased functional activity levels during mental representation of sequential finger movements. Two adjacent oblique planes were defined along the central sulcus of the left hemisphere, including the putative hand representation area of the primary sensorimotor cortex (14, 34, 35, 64, 106). Functional images from the same planes were then acquired using a high-resolution gradient-echo FLASH sequence (in plane resolution less than 2 mm; 4 mm slice thickness).

Each subject was asked to perform three different tasks sequentially: mental representation of a stationary visual scene (visual imagery-VI), mental representation of self-paced, sequential finger-to-thumb opposition movements of the right hand (motor imagery-MI), and actual execution of the same motor sequence (motor performance-MP). Visual imagery was taken as a reference state to control for possible aspecific effects related to imagery. Subjects were instructed to perform the motor sequence at a constant rate of about 2 Hz in a simple, fixed finger order (2-3-4-5-2-3-4-5), exerting a light pressure at each finger contact with the thumb. In a separate session, electromyographic (EMG) activity was recorded in each volunteer from surface electrodes overlaying the thenar eminence or flexor digitorum superficialis on the medial aspect of the forearm, while subjects performed the three tasks (VI, MI, and MP). Although a mild increase of EMG activity during MI was observed in some subjects, the integrated EMG data were not significantly affected by motor imagery in the whole subject population.

Significant increases in mean normalized fMRI signal intensities over values obtained during the control (VI) task were found in a region including the anterior bank and crown of the central sulcus, the presumed site of the primary motor cortex, both during actual motor performance (mean percentage increase, 2.1%) and during motor imagery (0.8%). Values obtained during motor performance were significantly higher than both of the other conditions. To investigate whether

these differences in mean fMRI signal intensities during MP and MI were related to the presence of spatially segregated neuronal populations selectively activated during one task, to a differential involvement of overlapping neural networks during the two tasks, or a combination of the two, the time course of signal intensities of pixels lying in the identified region was plotted against single- or double-step waveforms, where the steps of the waveform corresponded to different tasks. Pixels significantly activated during both MP and MI were identified in the majority of subjects; percentage increases in signal intensity during MI were on average 30% as great as the increases during MP. The pixels activated during both MP and MI represented a large fraction of the whole population activated during MP, and they were intermingled with pixels activated during motor performance only. Only one subject showed a small number of pixels activated during motor imagery only. These data extend the findings by another group (85) of an increase of activity in the contralateral right or left motor cortex in 4/6 subjects during imagery of a similar sequence of finger movements. Interestingly, the percentage change of activation during MI relative to that found during MP (30%) was identical in the two studies.

Both methodological factors and the kind of motor task may explain why this imagery-related activity in the perirolandic cortex has not been detected in early functional imaging studies. Levels of activation during imagery were relatively low compared to actual motor performance: therefore, they may have been undetected by imaging techniques characterized by lesser sensitivity and spatial resolution. Moreover, given the complexity of motor subsystems, differences in the pattern of activation of motor and premotor areas are to be expected when different kinds of motor acts are executed or imagined (1, 44, 83). In our study, a simple and predictable self-paced sequence of finger movements was employed, which can be easily implemented even without a training period. This kind of motor task may be viewed as an overlearned motor program (46) which is at least in part resident in neural populations in the precentral gyrus (30, 91). When more complex, learned sequences of finger movements must be retrieved, the supplementary motor area is more likely to be involved (31, 77, 82, 94).

These results suggest therefore that, at least for some kinds of movements, overlapping neural networks in the primary motor area are activated during mental representation and actual motor performance, supporting the hypothesis that brain networks underlying motor imagery overlap those involved in the preparation and execution of real motor acts (18, 43).

SUMMARY

Non-invasive functional magnetic resonance imaging (fMRI) mapping techniques sensitive to the local changes of blood flow, blood volume, and blood oxygenation which accompany neuronal activation have been widely used over the last few years to investigate the functional organization of human cortical motor systems, and specifically of the primary motor cortex. Validation studies have

demonstrated a good correspondence between quantitative and topographic aspects of data acquired by fMRI and positron emission tomography. The spatial and temporal resolution affordable by fMRI has allowed to achieve new important information on the distributed representation of hand movements in multiple functional modules, and on the intensity and spatial extent of neural activation in the contralateral and ipsilateral primary motor cortex in relation to parametric and nonparametric aspects of movement and to the degree of handedness. Neural populations with different functional characteristics have been identified in anatomically defined regions, and the temporal aspects of the activation during voluntary movement tracked in different components of the motor system. Finally, this technique has proved useful to deepen our understanding of the neural basis of motor imagery, demonstrating increased activity in the primary motor cortex during mental representation of sequential finger movements.

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