
Functional magnetic resonance imaging of the primary motor cortex in humans: response to increased functional demands

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Functional magnetic resonance imaging (fMRI) studies have been performed on 20 right handed volunteers at 1.5 Tesla using echo planar imaging (EPI) protocol. Index finger tapping invoked localized activation in the primary motor area. Consistent and highly reproducible activation in the primary motor area was observed in six different sessions of a volunteer over a period of one month. Increased tapping rate resulted in increase in the blood oxygenation level dependent (BOLD) signal intensity as well as the volume/area of activation (pixels) in the contralateral primary motor area up to tapping rate of 120 taps/min (2 Hz), beyond which it saturates. Activation in supplementary motor area was also observed. The obtained results are correlated to increased functional demands.

1. Introduction

Magnetic resonance imaging (MRI) is rapidly progressing beyond its conventional role of providing anatomical and metabolic information through MRI and magnetic resonance spectroscopy (MRS) to functional magnetic resonance imaging (fMRI). Functional MRI is emerging as a promising technique for the detection and assessment of cerebral pathophysiology, characterization and distinct regional mapping of human cognitive functions such as vision, motor, language, memory, etc. (Turner *et al* 1991; Kwong *et al* 1995; Kim *et al* 1994; Rao *et al* 1993; Ogawa *et al* 1993; Segebarth *et al* 1994; Haacke *et al* 1994, 1995; Moser *et al* 1996). Understanding of the brain functional areas, the identification of the regional activated sites, mapping the task performance within these areas, and the determination of the spatial distribution of

the process centres have long been the goal of neuroscientists. When compared with the other functional imaging modalities such as positron emission tomography (PET) (which has so far contributed most significantly to the functional brain mapping), fMRI has better S/N ratio and spatio-temporal resolution. Furthermore, unlike PET, fMRI does not use any ionizing radiation, thereby permitting repetitive studies to be made on the same subject. Therefore fMRI can be tailored to dynamic activation task paradigm within the same clinical session.

Control of movement is achieved via a complex series of interactions among the motor cortex, basal ganglia, thalamus, cerebellum and brain stem nuclei. From a very simple to a very complicated and precision motor task, the brain is able to control the muscles in the body in a precise and efficient way. Motor function is controlled by four distinct regions in the frontal lobes: the primary

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Abbreviations used: BOLD, Blood oxygenation level dependent; CBF, cerebral blood flow; fMRI, functional magnetic resonance imaging; EPI, echo-planar imaging; FOV, field of view; MRI, Magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, position emission tomography; rCBF, regional cerebral blood flow; SMA, supplementary motor area; S/N, signal to noise.

motor cortex, supplementary motor area (SMA), lateral premotor cortex and the cingulate motor area (figure 1). The primary motor cortex is responsible for direct production of movements via its outputs to the pyramidal tract. It receives inputs from several brain regions, including thalamus (which provides a link to the basal ganglia and cerebellum), supplementary and premotor area, and somatosensory cortex. Premotor area is especially important in behaviours and sensory guidance of movements. Supplementary motor cortex is active in the execution and planning of complex sequential movements (Lewine 1995). Studies of the SMA using PET have shown that it is involved in motor task sequencing and movement initiation (Passingham 1993), however, recently it has more been suggested that the SMA could be divided into two discrete areas: the pre-SMA and the SMA proper (Matsuzaka *et al* 1992). The SMA proper, is more directly involved in movement execution, whereas the pre-SMA, which receives inputs from the prefrontal cortex and the cingulate motor areas, might be responsible for movement decision making. Parietal areas are believed to provide spatial information for targeted movements.

Functional imaging relies on the detection of local physiological and metabolic changes (for example, blood flow, glucose and oxygen utilization) that are associated with the neuronal activity in the different regions of the brain. Small changes in oxygen utilization, usually of the order of 2 to 7%, can be detected with a specially designed susceptibility sensitive MRI method called blood oxygenation level dependent (BOLD) technique (Ogawa

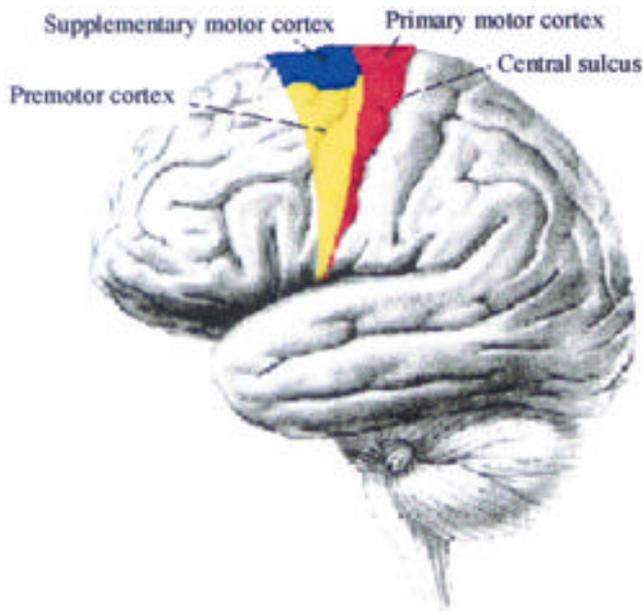


Figure 1. Locations of the primary motor cortex, premotor cortex and supplementary motor area.

et al 1992). This is based on the fact that oxygenated blood has different magnetic properties (diamagnetic) as compared with deoxygenated blood (paramagnetic) and hence different magnetic susceptibility. When neuronal activity increases, blood flow increases and more oxygenated blood is transported to the active neurones which exceed the corresponding oxygen consumption, resulting in an imbalance between oxygen supply and utilization. This results in the increase of effective transverse relaxation time ($T2^*$) and hence increased signal intensity in the local neuronal tissue on $T2^*$ sensitive MR pulse sequences. Ultrafast imaging techniques such as echo-planar imaging (EPI) (Stehling *et al* 1991) and turbo gradient echo (FLASH) (Kleinschmidt *et al* 1997) have been used extensively following the early experiments (Belliveau *et al* 1991), to detect changes in the cerebral blood flow (CBF) and oxygenation levels elicited by the neuronal activity. Both EPI and gradient echo (FLASH) sequences are sensitive to $T2^*$ changes. Though signal intensity is found to be higher in FLASH, EPI is still widely used and is considered a reliable technique with reduced imaging time and increased slice coverage (Fellner *et al* 1998). In a typical fMRI experiment, blocks of baseline and activation images are scanned periodically while the subject is at rest and during the performance of an activity such as cognitive or motor task. The activation image series is compared with baseline images (rest series) to detect the activated region. Various statistical methods (Ardekani and Kanno 1998) have been used for assessing these small and subtle changes arising due to neuronal activation. Recent reviews have elaborated the motor organization, functional aspects of motor cortex activation during contralateral and ipsilateral arm movements (Mattay and Weinberger 1999; Porro and Corazza 1999). The study of the response of the motor system with increased functional demands has been studied by various groups using fMRI and PET (Blinkenberg *et al* 1996; Rao *et al* 1996; Sadato *et al* 1997; Wexler *et al* 1997). The regional cerebral blood flow (rCBF) in the primary cortex has been reported to increase with repetition rate of simple finger movement, with saturation of rCBF at rates faster than 2 Hz, using PET and fMRI (Sadato *et al* 1996; Schlaug *et al* 1996). Other studies using fMRI and PET have shown a linear increase in the per cent change signal intensity of the primary motor area of the contralateral hemisphere with tapping rates of 1–4 Hz (Rao *et al* 1996; Sadato *et al* 1997), but tendency to decrease in the area of activation beyond 2 Hz. Though the finger movement is the simplest motor task, as the frequency of tapping is increased, it becomes complex, with amplitude, force and complexity not remaining the same. Different patterns of change in signal intensity with different tapping rates were reported. Also, extended finger tapping has not been mentioned exquisitely. Hence, the present study was undertaken.

The aim of this study is to standardize the measurement protocols and optimize the task paradigm for precise mapping of primary human motor cortex and its response to increased functional demands. The study consists of the following set of experiments, (i) to map the primary motor areas corresponding to finger movement in left and right hand, (ii) to test the reproducibility of the activation map, (iii) precise mapping of task activation in 3-dimension, and (iv) to study the activation signal in response to increased functional demands.

2. Materials and methods

Twenty right-handed volunteers (15 male and 5 female in the age group 20–40 years) were studied by the fMRI using BOLD technique and multi-slice EPI sequence.

2.1 Imaging protocol

Five para-axial slices parallel to the bicommissural plane through the fronto parietal cortex were acquired using single shot EPI (TE = 64 ms; flip angle = 90°; slice thickness = 3 mm; matrix 64 × 128; No. of measurements = 70; measurement interval = 3 s) with a scan time of 1 s/measurement. The in plane resolution was 3.28 mm × 1.64 mm with a total field of view of 210 mm. Prior to the acquisition of EPI images, shimming was performed to optimize the magnetic field homogeneity. Corresponding T1 weighted high-resolution images were collected with exactly the same slice orientation and slice position to compare the anatomy with functional activation. The FOV was the same for the functional studies, so as to co-register the functional (EPI) and anatomical (T1 weighted) images. The images were acquired using 1.5 Tesla whole body MRI system (Magnetom Vision, Siemens, Erlangen, Germany) using a circularly polarized head coil and 25 mT/m actively shielded gradient system. In an attempt to map precisely the primary motor cortex corresponding to index finger movement, 28–32 slices covering the whole brain were acquired in two normal volunteers to reconstruct functional maps in three orthogonal planes.

2.2 Task paradigm

Three cycles each of activated (index finger tapping in extended position) and control paradigms, preceded by a control phase of 10 measurements, were performed. Each cycle consisted of ten measurements for activation and control phase, resulting in a total of 70 measurements for complete study and the same experimental conditions were maintained in all the studies. Verbal commands were given to start and stop the motor task. The subjects were

visually monitored during the examination to confirm adherence to the experimental design. For testing the reproducibility, two volunteers (male, aged 20 and 27 years) were asked to perform the right index finger tapping over 6 sessions spread over a period of 4 weeks.

2.3 Tapping rates against activation

To study the changes due to increased functional demands, nine highly motivated volunteers (8 male and 1 female in the age group 20–40 years) were instructed to perform right index finger tapping at three different rates (40, 80 and 120 taps/min) and in four of them the task was carried out at five tapping rates (60, 90, 120, 150 and 180 taps/min). These subjects were requested to tap in synchrony with the sound of a metronome to guide them externally. A tapping device built inhouse was used to ascertain the rate and amplitude of tapping. The tapping device has a finger resting pad, which when pressed fully (against a non-magnetic spring) increments a mechanical counter. The metronome frequency and the counts from the tapping device correlated well (> 95%).

2.4 Post-processing

Acquired images were carefully examined for any head movement, and were then taken for the calculation of the functional maps generated pixelwise using a Z-score method and superimposed on high resolution anatomical T1 weighted images. Z-score is calculated by dividing the difference of the mean of the pixel intensities in activated and resting periods by the standard deviation of rest values.

3. Results

Five oblique (transverse to coronal) slices, as positioned on the sagittal scout image in figure 2a, were acquired to cover the motor cortex. Motor task (involving simultaneous movement of all the fingers of the left hand) revealed significant activation in the anterior and posterior margins of the central sulcus of the brain corresponding to the primary motor and sensory cortex of the right hemisphere (figure 2b). Consistent activation in the anterior margin of the central sulcus (primary motor cortex) of the contralateral hemispheres alone was seen in all the volunteers while performing left and right index finger tapping (figure 2c,d).

In the reproducibility (test-retest precision) study, two volunteers were instructed to perform the same repetitive right index finger tapping in six different sessions over a period of four weeks and exhibited highly localized activation in the primary motor area of the left hemisphere (figure 3).

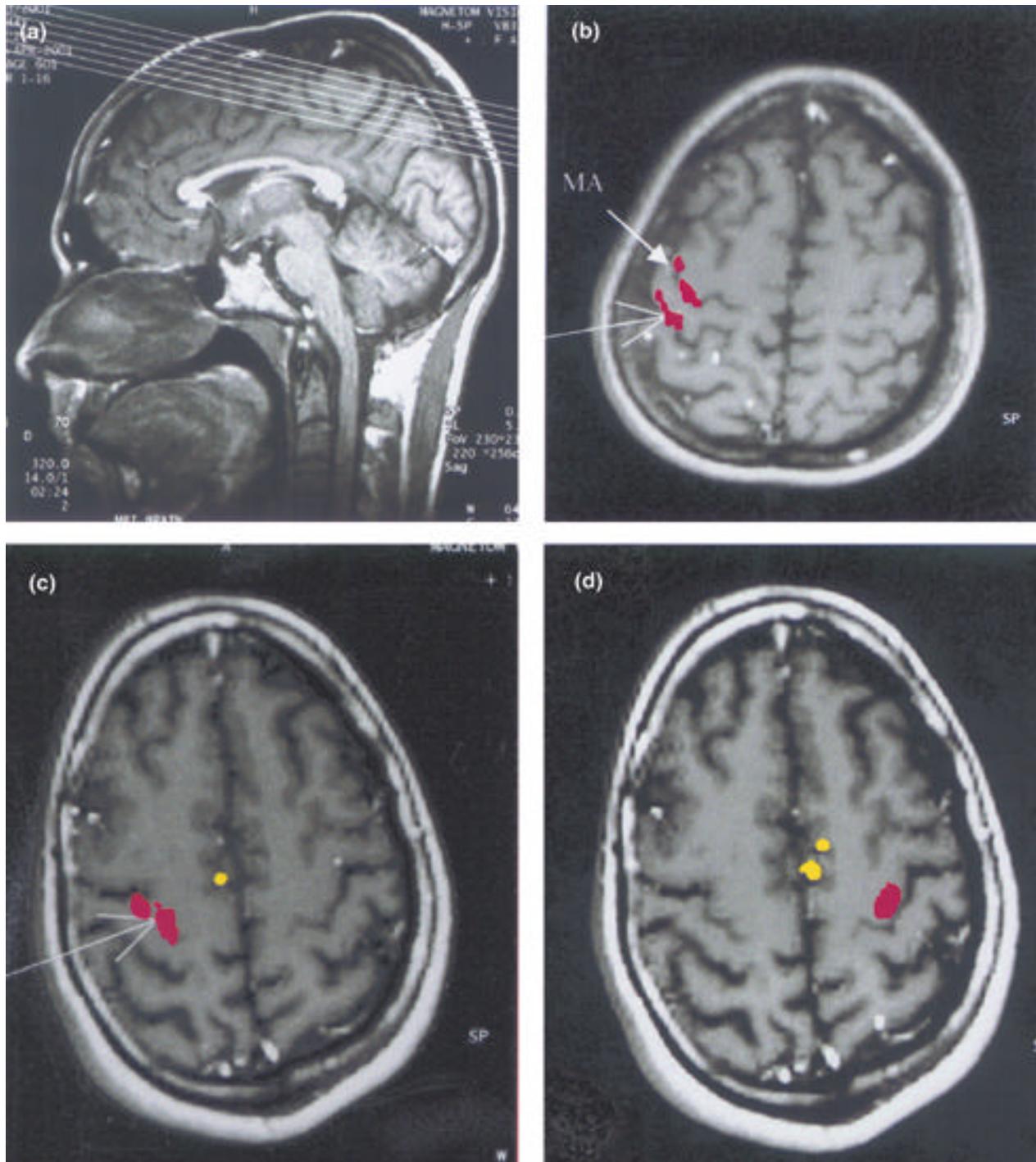


Figure 2. (a) Sagittal scout image showing the slice positioning of five T1 Weighted images. (b) Functional maps superimposed on a high resolution anatomical image corresponding to the movement of all the fingers of left hand (shown in red). Upper arrow indicates primary motor area and lower arrow shows the sensory area. Functional maps superimposed on a high resolution anatomical image corresponding to (c) left index finger and (d) right index finger (red indicates primary motor area; yellow shows the supplementary motor area).

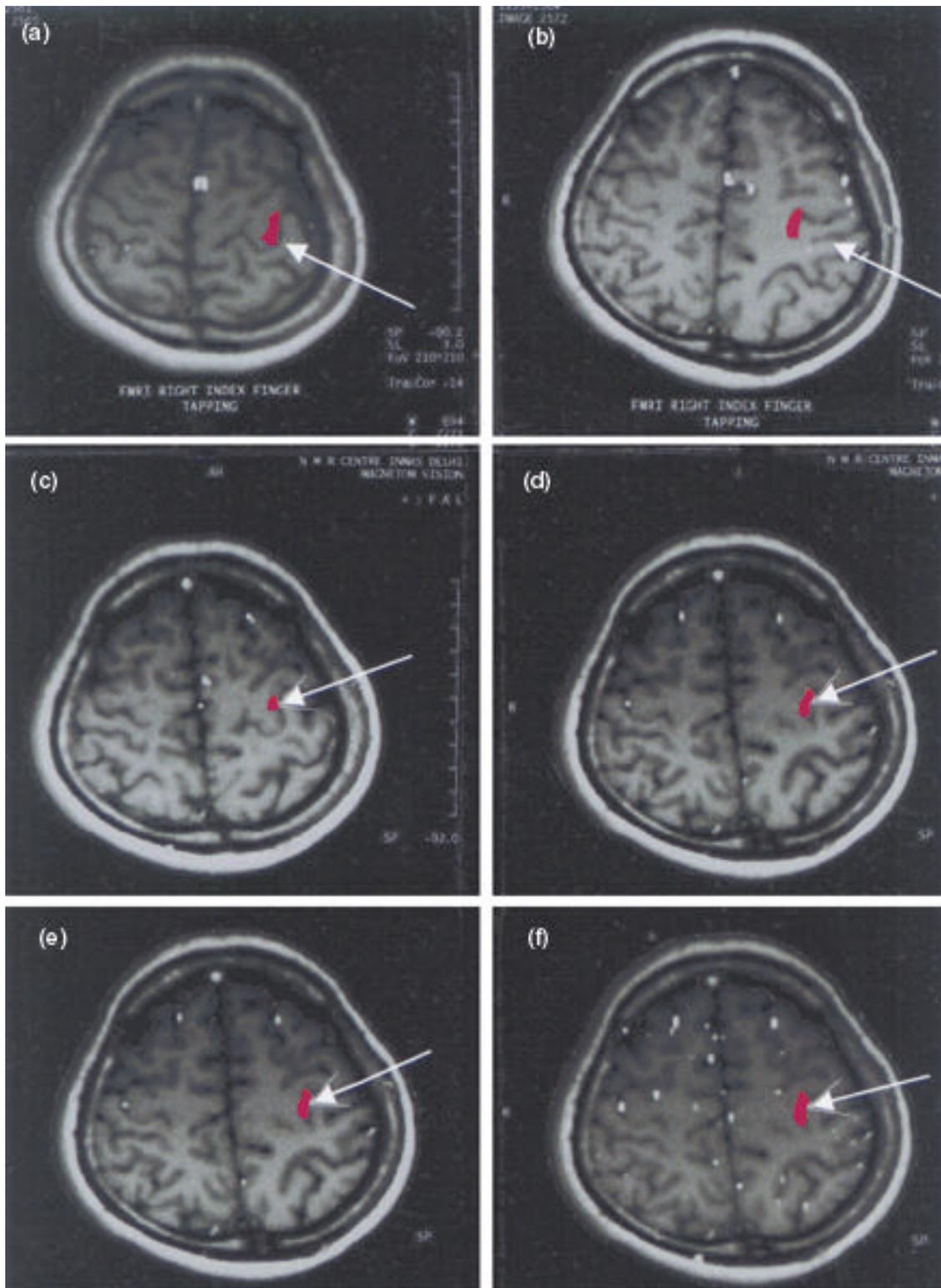


Figure 3. Functional maps of a volunteer at 6 different sessions (a–f) over a period of 4 weeks (arrows point to activation, in red).

Whole brain fMRI was performed in two volunteers with multi-planar reconstruction of the Z-score images and projections presented in the three orientations in an attempt to display the activation of the primary motor cortex in the three orthogonal (axial, coronal and sagittal) planes (figure 4). Considerable variability has been observed in the relative sizes of activated regions in different planes due to the extent to which regions were represented in the three imaging planes.

The responses of motor system to increased task performance were studied in five volunteers. Changes in signal intensity observed as a function of plots of the fMRI time course during resting and activation from regions of the activated pixels at three different tapping rates 40, 80 and 120 taps/min respectively are shown in figure 5a,c,e. It is clearly seen from these activity curves that the mean intensity and the number of the activated pixels is maximum at the tapping rate of 120 taps/min followed by 80 taps/min and 40 taps/min. The activation maps corresponding to the three tapping rates are shown in figure 5b,d,f. However, when the tapping rate increases, activation in the supplementary area also is observed besides primary motor cortex. The above study paradigm was redesigned on another four volunteers with five tapping rates of 60, 90, 120, 150 and 180 taps/min. The relationship between the tapping rate and per cent change in BOLD signal is shown in figure 6. The signal intensity and the number of pixels of activation show an increase till 120 taps/min. No significant changes beyond 150 taps/min were observed in three volunteers, whereas a slight decreasing trend in signal intensity was observed in one volunteer. It is clearly seen from figure 7 that the area of activation (number of pixels) increase as the tapping rate is increased to 120 taps/min while no further significant increase in the area of activation was apparent beyond 120 taps/min.

4. Discussion

The movement of all the fingers (folding the palm) has been a routine task reported in the literature, but we observed sensory cortex activation (figure 2b) during the process. To exclude the contribution due to sensory inputs, the volunteers were instructed to perform a motor task involving the tapping of index finger only, and avoid touching other fingers. Activation in the primary motor area in the contralateral hemisphere only was observed (figure 2c,d) and the absence of activated pixels in the posterior margins of central sulcus indicates the absence of sensory inputs, confirming the sensory activation was due to touching of fingers.

In the initial reproducibility study (figure 3), we observed a consistent activation in the primary motor

area. But, signal intensity and number of activated pixels varied over the six sessions due to the fact that frequency and force of tapping were not controlled. We could observe excellent reproducibility of image selection in 5 of 6 sessions, which is better than that observed by previous fMRI studies (Wexler *et al* 1997), where session-to-session reproducibility of image slice selection in 5 of the

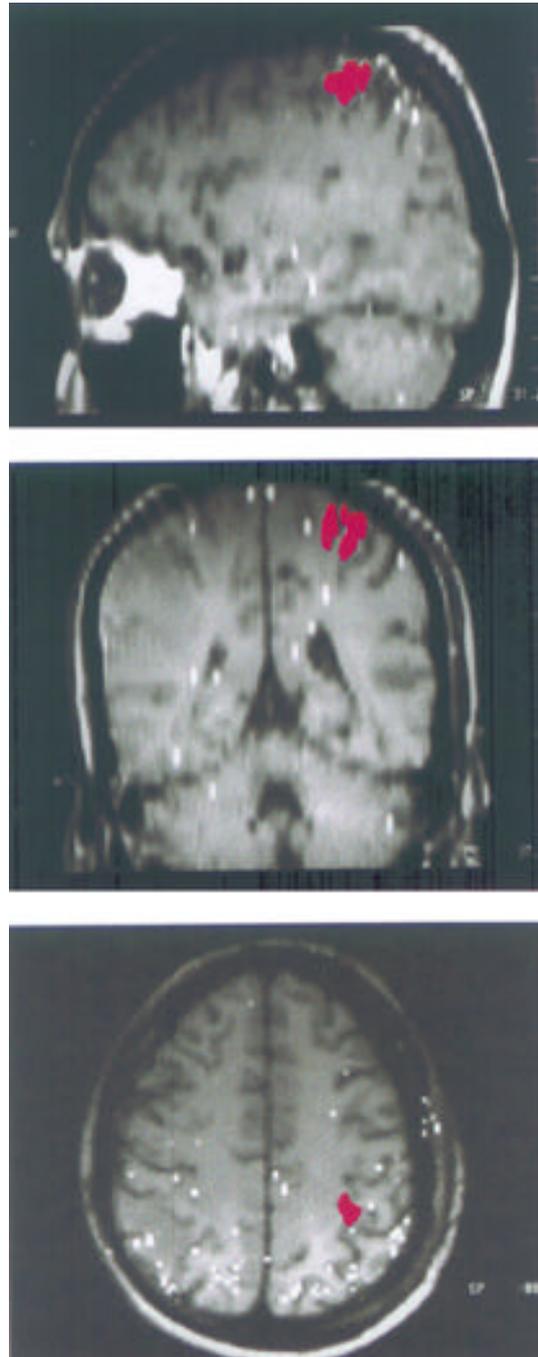


Figure 4. Activation maps in three orthogonal planes (shown in red).

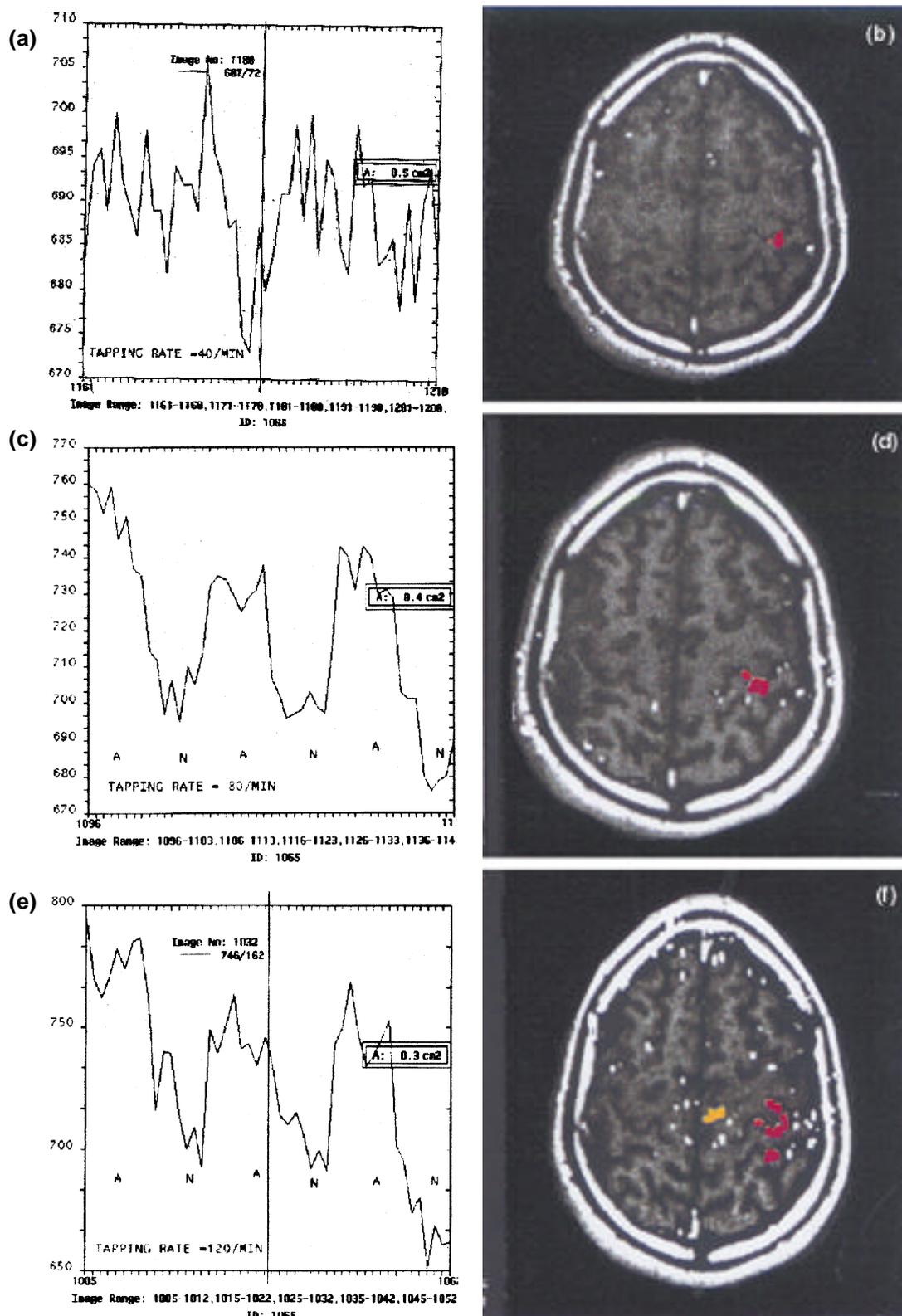


Figure 5. Plots of the activation signal during resting and activation of the fMRI time series (left) and functional maps (right) corresponding to right index finger tapping at three different rates (a, b) 40 taps/min, (c, d) 80 taps/min and (e, f) 120 taps/min.

9 sessions was reported. They have also observed that per cent signal changes for the cluster of activated voxels in the motor area ranged from 1.2 to 3.0% across sessions. Approximately 10% of voxels in each area showed clear task-related activation (Wexler *et al* 1997). Though venous contributions affect the signal in the motor cortex studies (Haacke *et al* 1994; Segebarth *et al* 1994; Yetkin *et al* 1996; Fellner *et al* 1998) in high resolution gradient echo and EPI studies, high test-retest precision and reliability are established in EPI studies. Our studies also show highly localized and reproducible activation in the contralateral primary motor area corresponding to index finger tapping, suggesting the greater reliability of the EPI technique for functional mapping of the human brain.

Our initial systematic studies with three tapping rates (40, 80 and 120 taps/min) exhibited the increase in the activation signal of the contralateral motor cortex as the tapping rate increased from slow to fast. There was no definitive trend in relative signal change at 40 taps/min (figure 5a). Possibly this slow movement rate may not be sufficient to evoke observable BOLD signal changes. Therefore, in subsequent four volunteers, we selected the tapping rates of 60, 90, 120, 150 and 180 taps/min. It is observed that as the functional demands increased, more neurones were recruited in the supplementary motor area besides primary motor cortex of the contralateral hemisphere. In a recent study where the effect of the stimulus characteristics such as rate, force and complexity of the motor task has been investigated (Wexler *et al* 1997), it has been observed that increase in the rate (45 taps/min to 90 taps/min) of motor task resulted in increase of the activation signal in the contralateral motor area and increased complexity resulted in activation of contralateral supplementary area. Our systematic studies with three tapping frequencies (60, 90 and 120 taps/min) confirm the increase in the activation signal of the contralateral motor cortex as the tapping frequency increased from slow to fast. The linear correlation between the frequency of tapping and the per cent BOLD signal changes observed in our study of four volunteers (figure 6) up to 120 taps/min (2 Hz) and a decrease in slope beyond 2 Hz is in agreement with the earlier PET and fMRI studies (Sabatini *et al* 1993; Sadato *et al* 1996; Schlaug *et al* 1996). Schlaug *et al* (1996) have shown that activity increases from 60 to 120 taps/min with activity unchanging from 120 to 180 taps/min. Blinkenberg *et al* (1996) have found that there is an optimum movement in frequency at 120 to 150 taps/min, reflecting a less complicated neuronal composition of the motor task execution of more trivial motor procedures, whereas Rao *et al* (1996) and Sadato *et al* (1997) have reported, change in regional CBF linearly correlated with the frequency of the movement up to 240 taps/min (4 Hz). The absence of any change in the signal intensity of the primary motor cortex when the tapping rate were further

increased to 150 taps and 180 taps/min, may be attributed to the saturation of blood oxygenation at the active neuronal site or to limitations of the technique. The decrease in signal intensity in one volunteer may be due to physical fatigue, since the volunteer expressed difficulty in tapping, though he continued the task till the end of study.

The results show a stronger effect of the frequency and amplitude of the motor task on the regional CBF changes in the contralateral primary motor area than in the supplementary motor area (Sabatini *et al* 1993). Activity in the contralateral MA appeared to be particularly sensitive to increase in the rate of movement (Schlaug *et al* 1996; Sadato *et al* 1996).

The primary response to increasing functional demands may be activation of cells that had shown little or no task-related activity at lower levels of demand, rather than further increasing the activity of tissue already active. Networks of cells constitute functional units in a probabilistic rather than a dedicated fashion. Increase in the intensity of activation in addition to increase in the volume of tissue showing clear task related activation has earlier been reported and attributed to increased force and complexity of movement (Wexler *et al* 1997). Recent PET studies show a positive correlation between the regional cerebral blood flow and the movement frequency principally in the primary sensorimotor cortex (Kawashima *et al* 1999). In another study, blood flow was significantly correlated with force of movement throughout the cortical motor system (Dettmers *et al* 1995). There have been different explanations regarding the increase in the number of active pixels with stimulus (Rao *et al* 1996), as it is assumed to be due to recruitment of different or additional muscle during execution of slow and fast tapping (Blinkenberg *et al* 1996). The area of activation within the primary motor cortex increased significantly with movement rate,

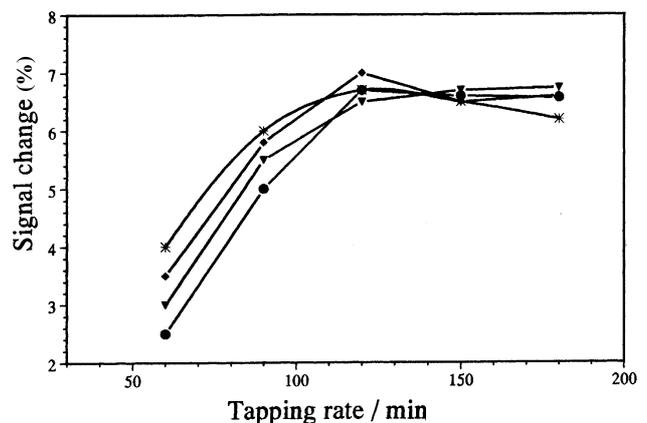


Figure 6. Percentage BOLD signal changes corresponding to right index finger tapping at five different rates (60, 90, 120, 150 and 180 taps/min) in four different volunteers.

but only between the 1 Hz (60 taps/min) condition and the faster movement rates (Rao *et al* 1996). This could be because, tapping at 60 taps/min resulted in fewer active voxels. In our study, 40 taps/min has not produced significant activity, which has been attributed to the fact that this tapping rate is insufficient to produce sufficient BOLD contrast. But we have observed significant increase in the area of activity with increased tapping frequency till 2 Hz and then decreases at 2.5 Hz. At lower task requirements, not all neurones are recruited and as the functional demand increases, the entire strip is activated (figure 7). This is in accordance to the earlier PET observation that the area of activation in the primary motor cortex decreased at frequencies above 2 Hz (Sadato *et al* 1996).

Functional MRI experiments present many experimental challenges considering the subject motion, complexity involved during the finger task and detection of subtle BOLD signal (< 7%). Our image processing software does not perform any data preparation before it is subjected to statistical analysis. All the studies were done on a limited area of the brain covering only the primary motor cortex. Whole brain experiments under highly controlled conditions to map activation pattern in the whole brain may throw light in the neural transmission related to the motor task. Study of glucose and oxygen utilization through PET and MRS would be required for detailed analysis of neuronal metabolism. Such studies will be very useful to investigate patients with motor and other functional defi-

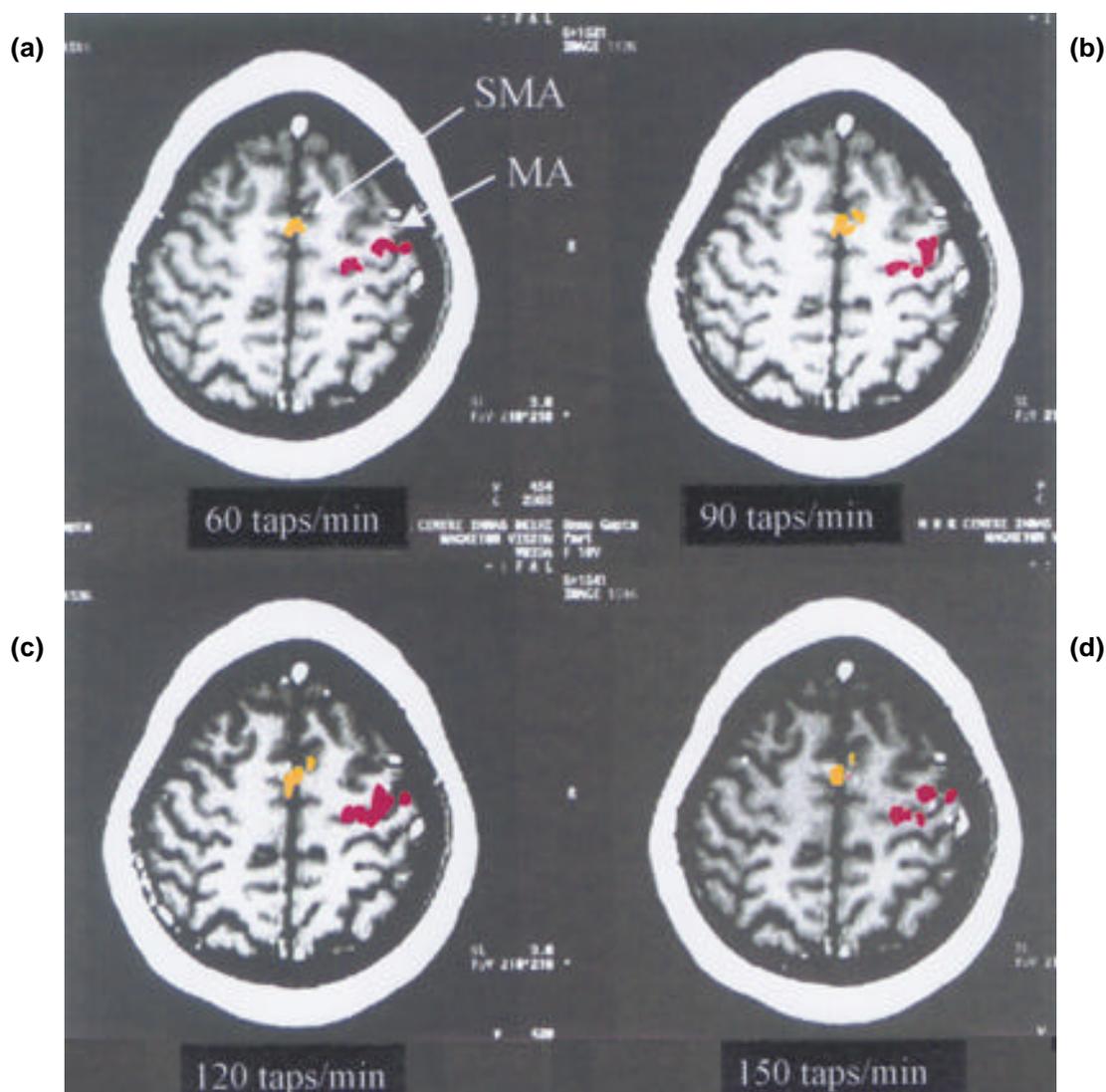


Figure 7. Functional maps (primary motor area in red and supplementary motor area in yellow) corresponding to (a) 60 taps/min, (b) 90 taps/min, (c) 120 taps/min and (d) 150 taps/min.

cits and may find widespread application for surgical and therapeutic management in these patients.

5. Conclusion

Our study establishes that the primary motor cortex can be mapped precisely and with high reproducibility on highly motivated volunteers using BOLD technique. The increase in the per cent change in the BOLD signal and area of activation corresponding to the increase in tapping rates suggests the increased energy demand and additional recruitment of neurones respectively, to supplement the increased functional demands. A comprehensive study of glucose, oxygen utilization using fMRI, MRS and PET would throw more light on the subject.

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