
REVIEW

Functional MRI in Human Motor Control Studies and Clinical Applications

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Functional magnetic resonance imaging (fMRI) has been a useful tool for the noninvasive mapping of brain function associated with various motor and cognitive tasks. Because fMRI is based on the blood oxygenation level dependent (BOLD) effect, it does not directly record neural activity. With the fMRI technique, distinguishing BOLD signals created by cortical projection neurons from those created by intracortical neurons appears to be difficult. Two major experimental designs are used in fMRI studies: block designs and event-related designs. Block-designed fMRI presupposes the steady state of regional cerebral blood flow and has been applied to examinations of brain activation caused by tasks requiring sustained or repetitive movements. By contrast, the more recently developed event-related fMRI with time resolution of a few seconds allows the mapping of brain activation associated with a single movement according to the transient aspects of the hemodynamic response. Increasing evidence suggests that multiple motor areas are engaged in a networked manner to execute various motor acts. In order to understand functional brain maps, it is important that one understands sequential and parallel organizations of anatomical connections between multiple motor areas. In fMRI studies of complex motor tasks, elementary parameters such as movement length, force, velocity, acceleration and frequency should be controlled, because inconsistency in those parameters may alter the extent and intensity of motor cortical activation, confounding interpretation of the findings obtained. In addition to initiation of movements, termination of movements plays an important role in the successful achievement of complex movements. Brain areas exclusively related to the termination of movements have been, for the first time, uncovered with an event-related fMRI technique. We propose the application of fMRI to the elucidation of the pathophysiology of movement disorders, particularly dystonia, which exhibits involuntary co-contraction of agonist and antagonist muscles and manifests abnormal posture or slow repetition of movements.

Keywords: *functional MRI, human motor control, clinical applications, motor termination, dystonia*

Introduction

Because of its excellent spatial resolution and the relatively high quality of the temporal information it provides, functional magnetic resonance imaging (fMRI) has been increasingly used to investigate human brain function since its emergence in 1990.^{1–4} Brain activation according to fMRI signals

is not a direct measurement of the synaptic activity or action potential of neurons, but it is based on the blood oxygenation level dependent (BOLD) effects, i.e., complex mechanisms caused by a combination of neural firing, oxygen consumption and regional cerebral blood flow (rCBF).^{5,6} Whereas the oxygen consumption caused by activities of the cortical neurons slightly increases (about 5%), the regional blood flow in the area increases much more (about 50%).^{7,8} Consequently, the relative concentration of capillary and venous deoxyhemoglobin in such a

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brain areas is reduced. Because deoxyhemoglobin is paramagnetic, it results in magnetic inhomogeneities and enhances the dephasing of spinning hydrogen protons. The reduction in the amount of deoxyhemoglobin lowers the rate of dephasing and causes the magnetic resonance signal (T_2^*) to decay at a slower rate. Thus, changes in oxygen consumption and rCBF lead to an increase in fMRI signals. The BOLD signal probably reflects post-synaptic activities (local field potentials) of neural cells in the brain rather than action potentials.⁹⁻¹¹ In the fMRI measurements, larger activated areas likely indicate activation of more cortical neurons, while a higher discharge rate for individual neurons is likely indicated by higher signal intensity.

Regardless of the different characteristics of motor tasks used in fMRI studies, multiple brain regions are similarly activated.¹²⁻¹⁴ Increasing evidence has suggested that the distributed neural systems work together in a networked fashion and process information involving millions of neurons.¹⁵ Even in a simple motor task, participation of multiple brain regions is necessary for planning and executing a motor action.^{16,17} Thus, anatomical connections between multiple motor areas need to be clarified, because hierarchical and nonhierarchical organizations of motor systems are essential for motor control. When we investigate more complicated tasks, it is important that we monitor and control elementary parameters such as movement rate, length and force, which may change cortical activation patterns. Therefore, in addition to addressing brain activation for complex motor tasks, we will review fMRI studies about the effects of such elementary movement parameters on brain activation.

Although complex movement comprises a combination of initiation and cessation of movements, so far little has been emphasized on the brain mechanism associated with motor termination. In this review article, we will focus on the neurophysiology of termination of movement in addition to initiation of movement. Finally, we will propose the possibility of clinical applications of fMRI to various movement disorders. In particular, an application of event-related fMRI to dystonia will be discussed.¹⁸

Experimental Designs in fMRI Study

Two different types of experimental designs are used in fMRI studies: block designs and event-related designs.¹⁹⁻²¹ In block-designed fMRI, for example, 30 s of a task (e.g., movement) and 30 s of rest are alternately performed. In the case of motor

control studies, this design is suitable for analyzing brain activity caused by sustained muscle contraction or a repetitive finger-movement task. By contrast, the more recently developed event-related fMRI technique that combines fast image acquisition such as echoplanar imaging and short repetition time makes it possible to map the second-by-second time course of the hemodynamic response related to a short-duration event.^{21,22} Therefore, the event-related design is applicable for investigating brain activation caused by a single movement, involuntary movements occurring intermittently at relatively long intervals (about 15 s), or a transient shift from one steady-state motor act to another.

According to the BOLD theory, fMRI signals do not directly reflect neural firings, but are related to changes in blood flow occurring at the level of capillaries and venules. Therefore, it appears to be difficult for the fMRI technique to distinguish signals of cortical projection neurons from those of cortical interneurons.²² In addition, Waldvogel et al.²³ discovered that inhibitory postsynaptic activity from cortical projection neurons likely escapes detection with fMRI measurement, and fMRI activation is mainly caused by excitatory postsynaptic activities. Another problem in fMRI measurement is that a pathological brain does not necessarily work in the same way as a normal brain in terms of blood flow, because autoregulation of cerebral blood flow may be impaired in the regions of a brain tumor, edema or infarction.²⁴

Anatomy of Motor-Related Brain Areas

Knowledge of the anatomical connections between motor-related brain areas is necessary in order to understand functional brain maps, because motor areas seem to work in a networked or cooperative manner to achieve meaningful movements (Fig. 1A, B). Most knowledge in this section has been obtained from primate studies. Compared to a primate brain, the human brain with its larger association cortices may have different anatomical and functional characteristics. Nonetheless, they share similar brain organizations in anatomy as well as physiology.²⁵ The M1 corresponding to the Bodmann's area 4 (BA 4), SMA (BA 6) and premotor area (PMA) (BA 6) are the most intensively studied motor areas, and they have direct connections with the spinal cord through the pyramidal tract.²⁶⁻²⁸ The M1 projects more neuronal axons to the pyramidal tract than either the SMA or PMA. The cingulate motor area (CMA; BA 23 and 24) also provides connections to the pyramidal tract.²⁸ Thus, each of several frontal motor cortical areas

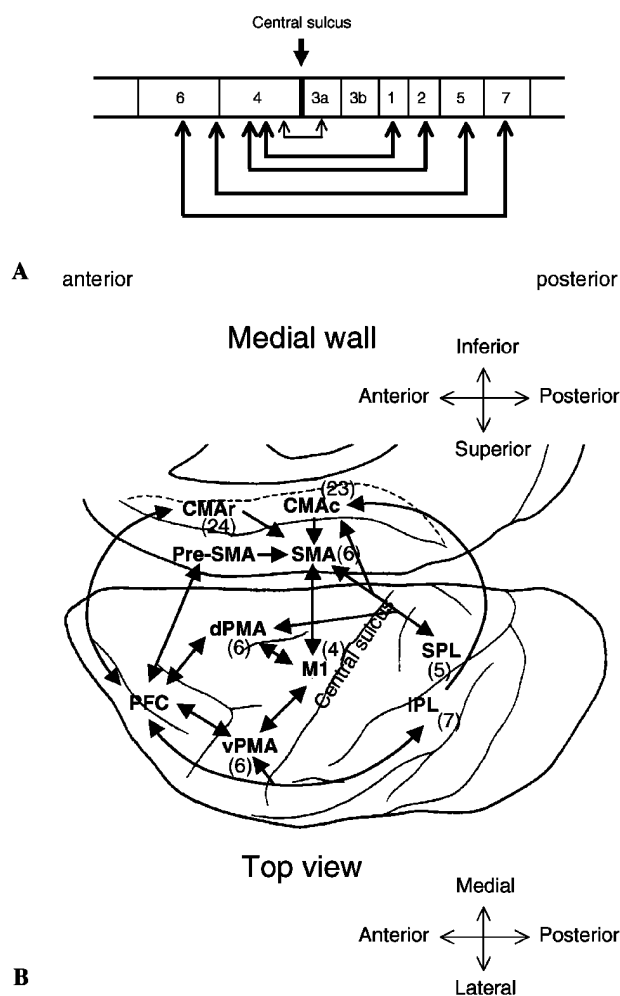


Fig. 1. Schematic illustrations of anatomical connections between motor areas

A: A sagittal section of gray matter showing reciprocal organization of frontal motor and parietal sensory cortices with respect to the central sulcus. The numbers indicate Brodmann's area (BA). Reciprocity exists between primary areas (BA 4 and BA 3, 1 and 2) as well as between nonprimary areas (BA 6 and BA 5 and 7). **B:** Interconnections between multiple motor-related cortices. The number in parentheses indicates Brodmann's area. M1: Primary motor cortex, SMA: Supplementary motor area, dPMA: Dorsal premotor area, vPMA: Ventral premotor area, CMAr: Rostral cingulate motor area, CMAc: Caudal cingulate motor area, PFC: Prefrontal cortex, SPL: Superior parietal lobe, IPL: Inferior parietal lobe

has the capability to influence spinal motor circuitry.

A general rule exists with regard to reciprocity between frontal motor and parietal sensory areas (Fig. 1A). Parietal areas near the central sulcus (CS) connect to frontal areas close to the CS, whereas more remote parietal areas communicate with the more remote frontal areas. This arrangement provides interconnections between the prima-

ry areas (M1 and S1) as well as between the nonprimary areas (frontal BA 6 and parietal BA 5 and 7). Only BA 3b, which is involved in an initial processing of cutaneous somatosensory information,^{29,30} does not have connections with the motor cortex. Although the M1 functionally is subdivided into face, arm and leg representations, each subdivision contains a highly overlapping, nontopographic internal organization; such extensive interconnections within each subdivision may serve as a substrate for synergetic contraction of multiple muscles of the face, arm or leg. Besides controlling movement dynamics such as the force of limbs,³¹ the M1 is engaged in movement kinematics such as production of the trajectory of arm movement.³²

Two nonprimary motor areas, SMA and PMA, are located in the medial and lateral portions, respectively, of BA 6. The SMA and PMA are reciprocally connected with the M1.^{28,33-35} The SMA is subdivided into rostral (pre-SMA) and caudal (SMA proper) parts.^{28,36} The SMA proper is connected to the M1 and spinal cord, whereas the pre-SMA lacks a direct connection with these structures. Instead, the pre-SMA receives strong inputs from the prefrontal cortex and projects to the somatotopic representation of an upper limb in the SMA proper,³⁷ suggesting a functionally superior role to the SMA proper. The SMA is concerned with the temporal organization of the sequential performance of multiple joint movements of the upper limb.^{36,38} Motor tasks requiring retrieval from motor memory³⁶ and bimanual coordination³⁹ also involve SMA activation. It has been shown that the PMA functions during the selection of motor actions according to visual cues⁴⁰ and the preparation of movements according to sensory instructions.⁴¹ The neurons in the dorsal aspect of the PMA (dPMA) show set-related activity in order to make a movement in response to the cue,^{42,43} whereas movement-related neurons are densely present in the ventral aspect of the PMA (vPMA). Thus, there seems to be dorsal-ventral organization of corticocortical projections between the premotor and parietal cortices (Fig. 1B); the BA 5 of the parietal lobe is directed towards the dorsal part of the PMA, while the BA 7 of the parietal lobe projects to the ventral part of the PMA. This suggests that dorsal and ventral regions of the nonprimary motor cortex have functionally segregated roles; the dPMA plays a more important role in conditional movement or in preparations for forthcoming movement, whereas the vPMA is involved in the executive aspect of externally guided movement.⁴⁴

Multiple areas exist in the distributed brain

regions engaged in the higher aspects of motor functions. These areas relay the visual, auditory or somatosensory information used in conditional motor acts. The posterior parietal cortex, temporal lobe, prefrontal cortex and insular cortex are likely involved in conditioning motor responses. The posterior parietal cortex seems to play an important role in visuomotor integration; the BA 5 of the posterior parietal cortex appears to link the high-order visual areas, and the M1 and PMA.⁴⁵ Visually guided reaching tasks require selective activation of the contralateral posterior parietal cortex.⁴⁶ Positron emission tomographic (PET) and lesion studies in humans^{47–49} also suggest a crucial role of the posterior parietal cortex, particularly the anterior bank of the intraparietal sulcus, in fine finger movements such as grasping. Therefore, the parietal BA 5 seems to encode movement kinematics, such as movement trajectory and direction, differently from the M1, which controls both movement dynamics and kinematics.

Two major subcortical structures, the basal ganglia (BG) and cerebellum (CBL), send information to motor cortical areas through the ventrolateral (VL) nucleus of the thalamus. Within the VL nucleus, the projections from the BG are anatomically separated from the CBL outputs. Most of the basal ganglial outflows go through VLm and VLo and project to the SMA.^{50,51} By contrast, cerebellar projections are directed at the M1 and PMA through the VLp, which contains nuclei X and VPLo.⁵⁰ The CBL seems to be involved in monitoring and optimizing movements with sensory feedback.^{52,53} The BG may be concerned with the selection of movements^{53,54}; the BG may inhibit competing motor programs that would otherwise interfere with the intended movements generated through cerebral and cerebellar mechanisms.⁵⁴

Parameters Affecting Activation in Motor Areas

Even for a simple movement task such as repetitive thumb opposition, multiple brain regions, including cortical and subcortical structures, are activated in fMRI measurements, as shown in Fig. 2. In this figure, normal subjects alternately performed 30 s of movement and 30 s of resting (block-designed fMRI). The primary sensorimotor area (SM1), BG and thalamic nuclei are activated contralaterally to the moving hand, while the CBL is activated on the ipsilateral side. The SMA shows the bilateral activation with contralateral preponderance. It should be noted that elementary

parameters such as movement rate, length and force affect the fMRI signals in the brain. When more complicated tasks are investigated in fMRI studies, such elementary parameters should be monitored and exactly controlled; otherwise, the expected results in studies employing complex tasks could be unreliable, because inconsistency in those parameters may alter the extent and intensity of motor cortical activation and confound interpretation of the findings obtained.

The movement rate determines the intensity and extent of the activation as well as the activated pattern of the motor areas. Two types of positive relationships have been reported between rate of finger movement and activation in the contralateral SM1: a linear increase in signal intensity and a step-wise increase.^{14,55,56} Rao et al.¹⁴ found that the signal change as well as the size of the activated cortical areas became larger with the increasing rate of movement. On the other hand, Jäncke et al.⁵⁶ found that the BOLD signal intensity shows a step-wise increase at 1.5 Hz, suggesting that dual motor control modes may be present in the separate frequency domains of movements.^{57,58}

With regard to the force, a purely isometric muscle contraction involves fMRI activation in the hand motor area.⁵⁹ Increased isometric force is reflected in the spread of a relatively constant fMRI signal over a wider area within the central sulcus, in the region of the motor hand knob.^{60,61} Compared to the repetitive execution of finger movements, the fMRI response is considerably smaller for the static finger flexion task.⁵⁹

As for the movement amplitude (movement length), a positive relationship exists between fMRI activation and movement amplitude in motor areas. Signal intensity in the SM1 significantly increases for the larger amplitude movement.⁶² Additional areas—including the SMA, PMA, insula and CBL—are frequently activated for the larger amplitude movement, but the small amplitude movement does not involve these areas.⁶²

Numerous fMRI studies have been conducted on more complex tasks, and the complexity of movements is an important determinant of expansion, intensity and patterns of motor cortical activation. In addition to the contralateral M1, finger-tapping in a sequential manner activates distributed brain regions including the SMA, ipsilateral M1, PMA bilaterally, S1 bilaterally, and superior parietal areas.^{13,63,64} The way in which the movement is paced also influences activation patterns of motor areas. The PMA is involved in relating external cues with motor acts, whereas the SMA appears to participate more in internally guided movement or

Activation of multiple brain regions during right finger tapping

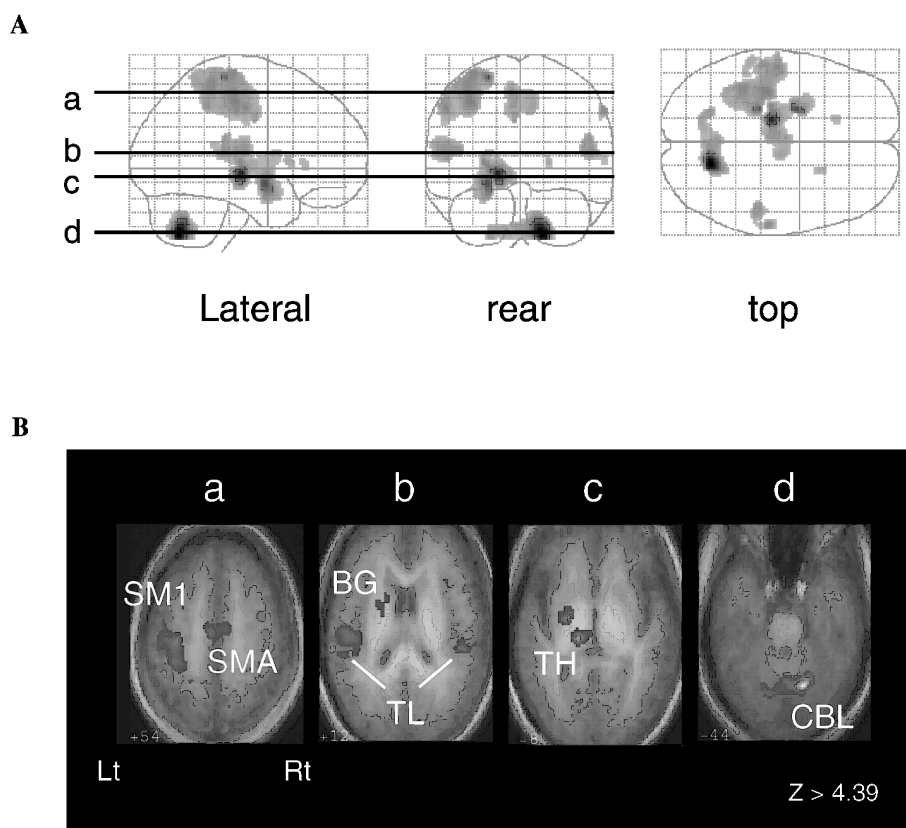


Fig. 2. Multiple brain areas activated for a simple finger-tapping task

A: Transparent projection displays (lateral, rear and top views) of the brain, which show regions commonly activated for eleven subjects performing right thumb opposition at 2 Hz. In the making of a common activation map, the image of each subject is normalized with respect to the standard brain coordinates.

B: Axial images of representative slices. Slices a, b, c and d correspond to the horizontal planes in Fig. 2A. In addition to the SM1 and SMA, the basal ganglia (b), medial and lateral thalamic nuclei (c) and cerebellum (d) are activated. The fMRI images were analyzed with statistical parametric mapping (SPM 99 from Wellcome Department of Cognitive Neurology, London, U.K.) implemented in Matlab (Mathworks, Sherborn, MA). SM1: Primary sensorimotor area, SMA: Supplementary motor area, BG: Basal ganglia, TL: Temporal lobe, TH: Thalamus, CBL: Cerebellum

planning of movement. Van Oostende et al.⁶⁵ compared the brain activation associated with the fingers-to-thumb tapping task that was paced in three different ways: (1) a fixed tapping sequence paced by external cues; (2) a random sequence paced by external cues; and (3) an internally selected sequence. Compared with the fixed tapping task, both randomly and internally paced tapping tasks yielded increased fMRI signals in the SMA, PMA and parietal areas. Rough or fine motor operation also influences brain activation patterns. Grasping

an object with the fingers requires two different ways of applying isometric power. During the power-grip task, all digits are used in a roughly palmar opposition grasp to hold the object. By contrast, in the precision-grip task, fine grip forces are elaborately applied between the tips of the index finger and thumb. The fMRI shows that the power grip induces greater cortical activation in the contralateral M1 and S1,¹⁷ whereas the precision grip causes larger activation in the ipsilateral PMA, bilateral rostral CMA, and at several locations in

Simultaneous recording of EMG and fMRI during voluntary muscle relaxation task

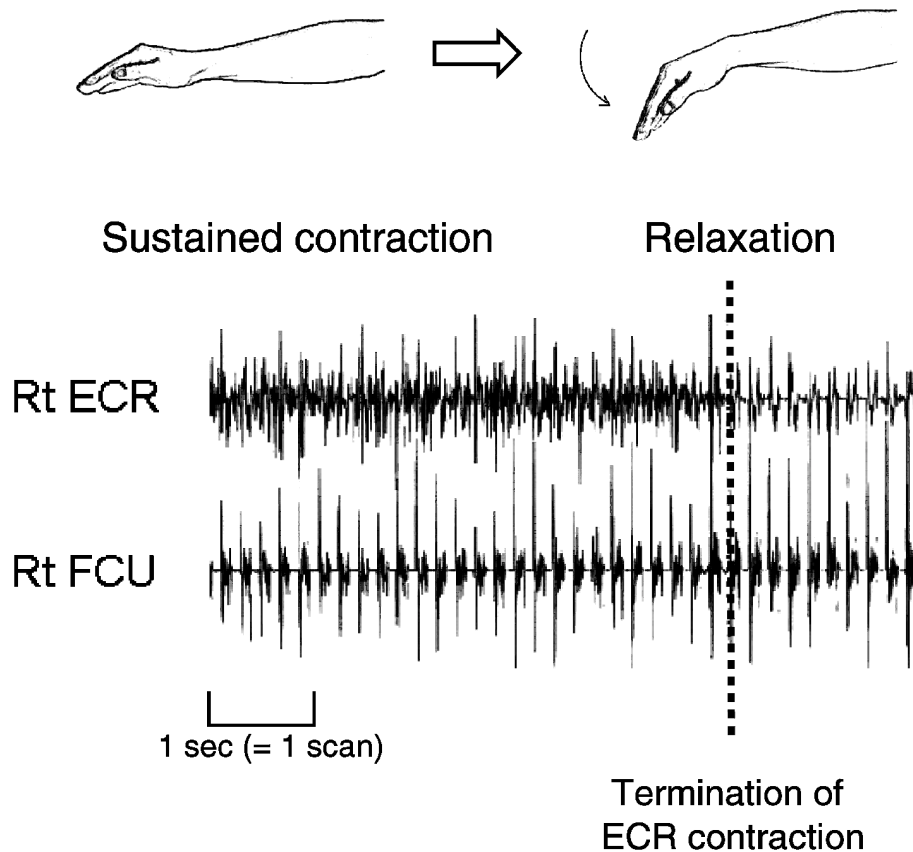


Fig. 3. Method by which the timing of motor termination was identified in the simultaneous recording of electromyography (EMG) and fMRI. The EMG activities from the right forearm muscles are shown together with the movement task. The EMG of the ECR muscle abruptly disappeared at the moment of motor termination (shown by the dotted line). Although there are many artifacts due to radiofrequency pulses, the EMG was observable during the fMRI scan. ECR: Extensor carpi radialis, FCU: Flexor carpi ulnaris.

the bilateral posterior parietal and prefrontal cortices.¹⁷ Widely distributed areas in the bilateral hemispheres appear to participate in the control of the precision grip task.

Motor Termination

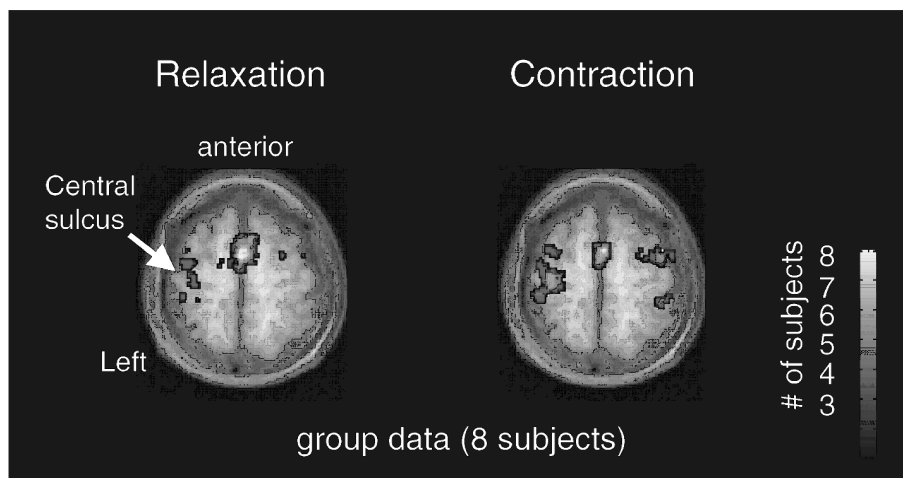
Although neural mechanisms for initiating and maintaining movements have been intensively investigated, so far little attention has been paid to neural mechanisms of motor termination.^{18,22} In order to successfully perform the complex movements commonly used in our daily motor repertoires, ongoing movements have to terminate and

move on to the next motor action. Clinically, moreover, some movement disorders manifest impaired processes in voluntary termination of movement or muscle contraction. Hence, delineating the brain mechanisms of motor termination can help to provide therapeutic approaches to movement disorders such as dystonia, myoclonus and epilepsy. In these disorders, patients have difficulty relaxing abnormal co-contraction of muscles or terminating hyperactive movements.

It is impossible to distinguish signals associated with muscle relaxation from those associated with muscle contraction in block-designed fMRI. In block-designed fMRI, contamination of fMRI

Brain activation associated with voluntary muscle relaxation and contraction

A



B

fMRI signal changes

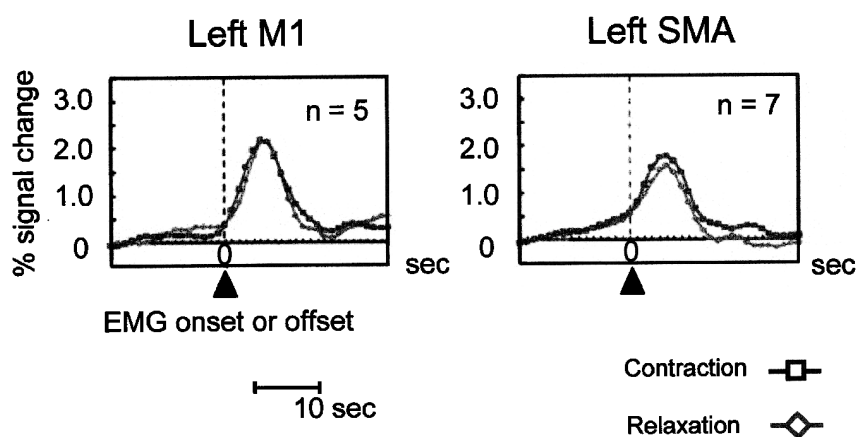


Fig. 4. **A:** Activated areas in the M1 and SMA are shown for eight normal subjects performing muscle relaxation and contraction tasks. The areas commonly activated in three or more subjects are illustrated. Both M1 and SMA are activated in the muscle relaxation and contraction tasks. **B:** Mean changes in signal intensity between relaxation and contraction are compared in the M1 and SMA. Both areas show similar activation for the muscle relaxation and contraction tasks. Data were analyzed with the event-related fMRI technique.

signals from muscle contraction is unavoidable because the subject needs to move a body part (e.g., hand) to set up the initial posture for the next muscle relaxation trial. Toma et al.²² employed an event-related fMRI technique to separately record the BOLD signals associated with motor initiation or termination (Figs. 3 and 4). For the relaxation task, the subject relaxed the wrist extensor muscles and allowed the hand to succumb to gravity after having kept the right hand horizontal by maintaining moderate contraction of these muscles (Fig. 3).

For the contraction task, the subject extended the right wrist from the same initial position of the right hand as in the relaxation task. As a result, both the muscle relaxation and contraction tasks involved transient activation in the M1 and SMA with similar signal intensity (Fig. 4B), and the activated volume in the SMA was significantly larger for the relaxation task than for the contraction task (Fig. 4A). They concluded that voluntary muscle relaxation transiently activates the M1 and SMA in a manner similar to voluntary muscle contraction,

Focal hand dystonia vs. Normal subject

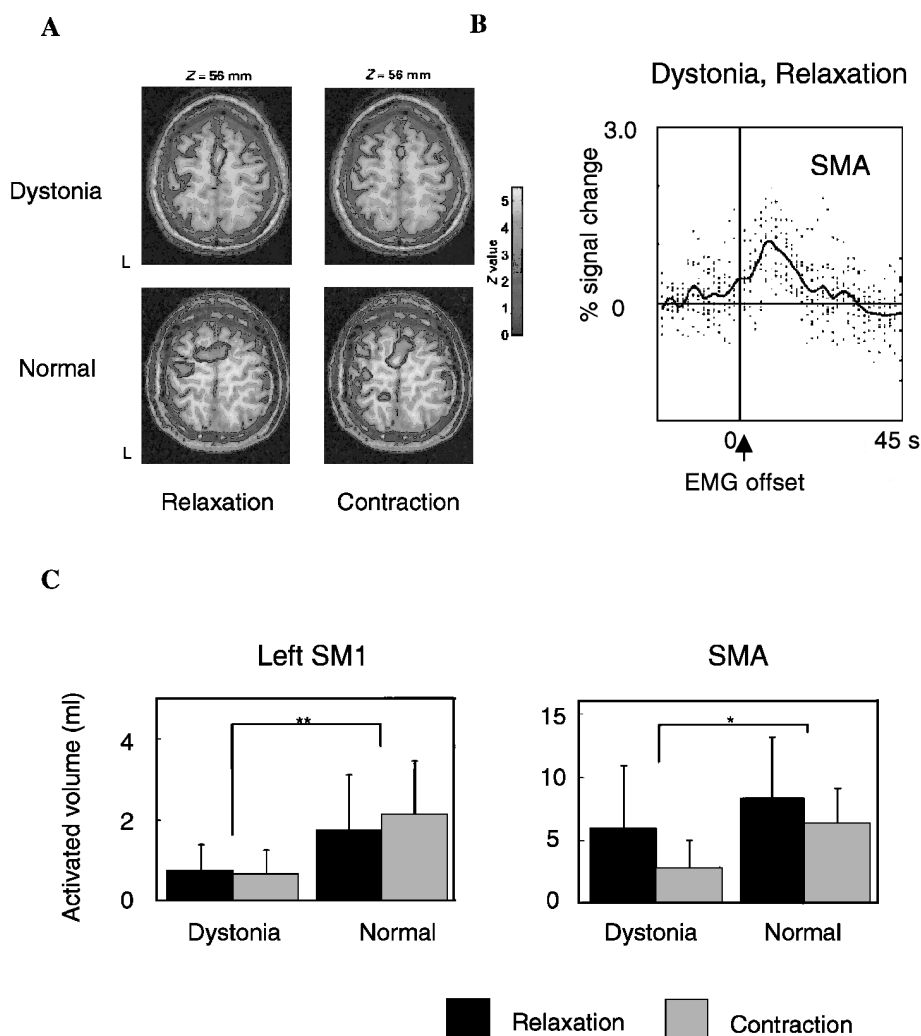


Fig. 5. Application of event-related fMRI to dystonic patients

A: Comparison of activated volume in motor cortical areas in a patient with dystonia and a normal subject in the muscle relaxation and contraction task. Data are from a single representative subject. In both tasks, the activated areas in the M1 and SMA are smaller for dystonia than for the normal control. **B:** Time course of the fMRI signals in the SMA of the dystonic patient in the muscle relaxation task. A solid line indicates a mean signal change across ten trials, which are shown with dots. Note that a transient signal change time-locked to EMG offset is observable even in a single trial. **C:** Group data from eight patients and twelve healthy volunteers, demonstrating that activated volumes in the contralateral SM1 and SMA are greater in the healthy volunteers than in the dystonic patients. * $P < 0.05$, ** $P < 0.005$.

From Oga et al. (2002) with the permission of the Oxford University Press.

and the SMA may play an important role in muscle relaxation.

Clinical Applications of fMRI

To identify the location of the M1 (such as the hand motor area), the recording of repetitive hand

movements at a fast rate by means of block-designed fMRI seems to be the most useful approach because such movements lead to robust activation in the M1. In the motor cortex, the preoperative and intraoperative cortical monitoring validates the results of fMRI examination⁶⁶; because these two methods correlate well, fMRI could

be a useful tool for the noninvasive evaluation of brain tumors before surgical resection. On the other hand, event-related fMRI is a technique for detecting transient activation in the brain, so it may be applicable to the detection of the brain area responsible for epileptic jerking, cortical myoclonus or tics occurring intermittently at relatively long intervals.

Dystonia is a movement disorder characterized by involuntary co-contraction of agonist and antagonist muscles, which causes abnormal posture or twisting and slow repetition of movements.⁶⁷ Patients with dystonia show difficulty in voluntarily terminating the contraction of irrelevant muscles. Previous electroencephalographic (EEG) studies in focal hand dystonia have suggested decreased activity in the central region contralaterally to the moving hand during either muscle relaxation⁶⁸ or contraction.⁶⁹ Although these observations are suggestive of hypoactivity, possibly in the M1, the impaired regions within the brain have remained unknown due to the poor spatial resolution of EEG measurement. The studies using PET, which provides good spatial resolution, reported underactivation of both SM1 and SMA in focal hand dystonia.^{70,71} In the PET studies, however, both muscle relaxation and contraction were intermingled and inclusively investigated, making it difficult to determine whether the cortical hypoactivity was from muscle relaxation or contraction. Oga and coworkers¹⁸ applied an event-related fMRI technique to reveal whether muscle relaxation, muscle contraction or both are impaired in patients with focal hand dystonia. The same relaxation and contraction tasks used in the study by Toma et al.²² were used in the study. As a result, it was successfully demonstrated that, in dystonia, brain activation is impaired in both muscle relaxation and contraction (Fig. 5). By separately imaging brain activation caused by muscle relaxation and contraction, they showed that activated volume in the contralateral SM1 and SMA is significantly smaller in the dystonia group than in the age-matched normal human group in both the muscle relaxation and contraction tasks (Fig. 5C).

For the past couple of years, pathophysiological mechanisms of movement as well as cognitive and psychiatric disorders have been increasingly studied with fMRI. Impaired fMRI activation in multiple brain regions has been reported in Parkinson's disease. Parkinsonian shows underactivation in the rostral SMA and overactivation in several brain areas including the caudal SMA, SM1 and lateral premotor and parietal cortices.⁷² After levodopa therapy, such impaired activation is normalized in

the rostral SMA and hyperactivation is decreased in the SM1, lateral premotor and superior parietal cortices.⁷³ Apart from Parkinson's disease, fMRI has been applied to disorders such as Alzheimer's disease and schizophrenia.^{74,75}

Conclusion

Since its emergence in the early nineties, fMRI has been used intensively to uncover functional human brain maps thanks to its good spatial and temporal resolution. Evaluation of brain function with fMRI has contributed significantly to the noninvasive elucidation of physiological mechanisms associated with human motor control. Efforts to devise clinical applications of fMRI will disclose the pathophysiology of various movement-disabled disorders.

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