Human Brain Activation During Sustained and Intermittent Submaximal Fatigue Muscle Contractions: An fMRI Study

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Departments of 1Biomedical Engineering, the Lerner Research Institute and 2Physical Medicine and Rehabilitation, The Cleveland Clinic Foundation, 44195; Departments of 3Physics and 4Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio 44106

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Liu, Jing Z., Zu Y. Shan, Lu D. Zhang, Vinod Sahgal, Robert W. Brown, and Guang H. Yue. Human brain activation during sustained and intermittent submaximal fatigue muscle contractions: an fMRI study. J Neurophysiol 90: 300–312, 2003. First published March 12, 2003; 10.1152/jn.00821.2002. During prolonged submaximal muscle contractions, electromyographic (EMG) signals typically increase as a result of increasing motor unit activities to compensate for fatigue-induced force loss in the muscle. It is thought that cortical signals driving the muscle to higher activation levels also increases, but this has never been experimentally demonstrated. The purpose of this study was to quantify brain activation during submaximal fatigue muscle contractions using functional magnetic resonance imaging (fMRI). Twelve volunteers performed a sustained handgrip contraction for 225 s and 320 intermittent handgrip contractions (~960 s) at 30% maximal level while their brain was imaged. For the sustained contraction, EMG signals of the finger flexor muscles increased linearly while the target force was maintained. The fMRI-measured cortical activities in the contralateral sensorimotor cortex increased sharply during the first 150 s, then plateaued during the last 75 s. For the intermittent contractions, the EMG signals increased during the first 660 s and then began to decline, while the handgrip force also showed a sign of decrease despite maximal effort to maintain the force. The fMRI signal of the contralateral sensorimotor area showed a linear rise for most part of the task and plateaued at the end. For both the tasks, the fMRI signals in the ipsilateral sensorimotor cortex, prefrontal cortex, cingulate gyrus, supplementary motor area, and cerebellum exhibited steady increases. These results showed that the brain increased its output to reinforce the muscle for the continuation of the performance and possibly to process additional sensory information.

INTRODUCTION

It is a common experience that when one performs a submaximal motor task repetitively (such as shoveling snow) or resists against a submaximal load for a long time (as when carrying a suitcase) muscle fatigue develops, which is reflected by a gradually increasing effort to perform the same task. Because fatigue impairs the muscles’ ability to generate force (for review: Bigland-Ritchie 1981; Enoka and Stuart 1992), the person eventually may not be able to continue the task, even with maximal effort, because of severe fatigue or exhaustion.

An increase in voluntary effort during the prolonged performance of a submaximal motor task has been indirectly indicated by increases in electromyographic (EMG) signals recorded from the performing muscles (Fuglevand et al. 1993, 1995; Löscher et al. 1996; Yue et al. 1997), which suggests that the nervous system attempts to recruit additional motor units to compensate for the loss of force. However, enhancement of effort during submaximal muscle contractions has never been shown directly by data recorded from the brain. Thus it is not clear whether an increase in one’s effort to continue the performance accompanies an elevation in the level of brain activation to drive the muscle (to recruit more motor units). Knowing how the brain modulates muscle fatigue or how information about fatigue affects brain activities in healthy humans may help explain why fatigue is so prevalent in patients with neurological disorders (Gandevia 2001; McComas et al. 1995). Electrophysiological (Siemionow et al. 2000) and neuroimaging (Dai et al. 2001; Dettmers et al. 1995) studies have reported a proportional relationship between cortical signals and exerted joint force in human subjects, indicating that brain signals are positively correlated to voluntary effort, as a higher level of effort is required for exerting greater muscle force.

Based on the findings that EMG signals increase during repetitive exertions of submaximal force or a prolonged submaximal muscle contraction to resist a constant load and that brain signals increase with enhanced voluntary effort, we hypothesized that muscle fatigue resulting from sustained or intermittent submaximal muscle contractions is associated with a progressive increase in the cortical signals for reinforcing the descending command to recruit additional motor units and/or for processing increased flow of sensory information to the brain. Furthermore, we hypothesized that the primary sensorimotor cortex would show a sign of “fatigue” by ceasing the rise of its activation level as muscle fatigue becomes severe. This hypothesis is based on our previous finding that functional magnetic resonance imaging (fMRI) signals of the sensorimotor cortex plateaued when voluntary muscle activities increased from a relatively high level to the next higher level (Dai et al. 2001).

The recent development of a powerful neuroimaging method, i.e., fMRI, makes the investigation of this problem possible (Kim et al. 1993; Kwong et al. 1992; Liu et al. 2002a; Ogawa et al. 1993; Yue et al. 2000). The purpose of this study was to determine brain activation level in the primary sensorimotor and higher-order cortical regions during sustained and intermittent submaximal fatigue muscle contractions: an fMRI study.
force/EMG and fMRI brain signals were collected and performed the two tasks both in the MRI machine while data of ner. The two sessions were separated by at least a week. The subjects lasted 960 s, consisting of intermittent (dynamic force, DF) handgrip contractions at 30% MVC level men, age = 33.1 ± 10.8 yrs, 11 right-handed and 1 left-handed). The experimental procedures were approved by the Institutional Review Board at the Cleveland Clinic Foundation. All subjects gave informed consent prior to their participation. All subjects performed two motor tasks in two sessions while their brains were imaged by fMRI. Preliminary results have been reported in abstract form (Liu et al. 1999, 2000b).

METHODS

Subjects and motor tasks

Twelve healthy subjects participated in the study (8 men and 4 women, age = 33.1 ± 10.8 yrs, 11 right-handed and 1 left-handed). The experimental procedures were approved by the Institutional Review Board at the Cleveland Clinic Foundation. All subjects gave informed consent prior to their participation.

All subjects performed two motor tasks in two sessions while their brains were imaged by fMRI: sustained (static force, SF) handgrip experiments. Twelve baseline/rest (OFF) fMRI scans were collected first; 92 (ON) scans were then collected continuously during the task performance period. B: protocol for the dynamic force (DF) handgrip experiments. After collection of 12 OFF scans, 7 sets of ON scans were collected periodically. Each set consisted of 12 scans, with a waiting period of ~2-min between any 2 consecutive sets.

intermittent handgrip contractions at 30% maximal voluntary contraction (MVC) level using fMRI. Preliminary results have been reported in abstract form (Liu et al. 1999, 2000b).

FIG. 1. Schematic illustration of the functional magnetic resonance imaging (fMRI) experimental protocols. A: protocol for the sustained static force (SF) handgrip experiments. Twelve baseline/rest (OFF) fMRI scans were collected first; 92 (ON) scans were then collected continuously during the task performance period. B: protocol for the dynamic force (DF) handgrip experiments. After collection of 12 OFF scans, 7 sets of ON scans were collected periodically. Each set consisted of 12 scans, with a waiting period of ~2-min between any 2 consecutive sets.

Force measurement

Handgrip force was measured by a system that consisted of a handgrip device, a pressure transducer [EPX-N1 250 PSI (CNL&H = ±0.5%, full-scale linearity >99%), Entran Devices, Fairfield, NJ], a 30-ft nylon tube (3-mm diam) connecting the handgrip device and the transducer, a water reservoir (which served as the water supplier of the hydraulic system), and a custom-built signal amplifier (DC-50 Hz) (Liu et al. 2000a). During the fMRI experiment, subjects gripped the handgrip device to match the target force provided by a visual feedback system (see following text). The handgrip device was a soft plastic bottle that could be comfortably gripped by hand (Liu et al. 2002b). The force applied by handgrip was sensed and converted to voltage signal by the pressure transducer in the hydraulic system. The output of the transducer was directed to the amplifier and then to an input channel of the Spike 2 data-acquisition board (version 3.05, Cambridge Electronic Design, Cambridge, UK), which transferred the voltage data to a laptop computer. The sampling rate for force data was 100 Hz. A sampled time course of force during the dynamic force task is displayed in Fig. 2A. Before each experiment, the MVC handgrip force and EMG were measured. These MVC data were later used for normalizing the force and EMG signals recorded during the fatigue contractions.

EMG measurement

Surface EMG signals were recorded from the following four muscles during the handgrip contractions: flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP), and extensor digitorum (including the extensor indicis, ED) in the right arm and FDS in the left arm. Bipolar electrodes (Ag-AgCl, 8-mm recording diameter, In Vivo Metric, Healdsburg, CA) were attached on skin overlying each of the four muscles. The muscles were identified by palpating the skin when subjects flexed and extended the fingers. A reference electrode was placed on the skin overlying the lateral epicondyle near the elbow joint of the right arm. The electrode wires were effectively shielded by multiple layers of shielding and connected to the custom-built amplifiers (10–3,000 Hz) located outside the MRI room (Liu et al. 2000a, 2002a). The EMG data were recorded at a sampling rate of 1,000 Hz to the laptop computer by the Spike 2 data acquisition system. In Fig. 2B, the EMG data corresponding to the force in Fig. 2A are displayed. High-quality EMG signals could be measured during each brief gap separating adjacent fMRI scans (Liu et al. 2000a, 2002a). One of these gaps has been expanded in Fig. 2C to show the actual EMG signals in the gap.

Because our MRI environment-adapted EMG measurement system has only four channels, it was not possible to record EMG signals

FIG. 2. Sample force and electromyographic (EMG) data recorded during an intermittent DF handgrip fMRI experiment. A: a sample period of force time course. B: the corresponding EMG data in 1 of the 4 channels. C, noise caused by the fMRI pulse sequence, each 1 corresponding to 1 fMRI scan of a whole brain volume (20 slices). The gaps that were covered by stabilized force time courses were selected, as indicated ( ), and were used in the EMG data analysis. C: enlarged view of 1 of the gaps between consecutive fMRI scans. The middle parts (~120 ms) of the EMG signals in the gaps were clean and used for data analysis.
from muscles other than the prime movers and their antagonists during the fMRI experiments to detect whether they changed their activities during the fatigue process. However, because these activities may affect fMRI-measured cortical signals, it is also important to quantify the activities of the nonprime mover muscles. To address this issue, we recorded surface EMG signals from 10 muscles of each of the 12 subjects in two separate sessions (1 motor task per session) in a non-MR environment. The two motor tasks were the same as in the fMRI experiments. For the SF experiment, a target line (30% MVC force) was displayed on an oscilloscope, and the subject was instructed to match the target as closely as possible. For the DF experiment, a series of traveling visual cues, i.e., a waveform of repetitive 2-s on (target force) and 1-s off (baseline), were displayed on the oscilloscope screen, and the subject exerted handgrip force to match the target during the on periods and relaxed during the off periods. The 10 muscles were: FDS, FDP, ED, first dorsal interosseous (FDI), biceps brachii (BB), deltoid (DT), and triceps brachii (TB) of the right arm and FDS, ED, and BB of the left arm. Subjects assumed a similar supine position and gripped the same force measurement device as in the fMRI experiments during the tasks. The EMG and force data were acquired using the above-mentioned devices and saved on the hard disk of the laptop computer. At the beginning of each experiment, a brief MVC (~5 s) involving each muscle was performed, and the MVC EMG was recorded. These MVC EMG data of each muscle were used in the data analysis to normalize EMG data of the same muscle obtained during the fatigue tasks.

Visual feedback

In the fMRI experiments, a visual feedback system was used for subjects to perform the force-matching tasks. This system included a Silent Vision unit (SV-2200, Avotec, Jensen Beach, FL), a video camera, and an oscilloscope (Liu et al. 2000a, 2002a). On the oscilloscope screen, the force output and the target line (30% MVC) were displayed in real-time. The video camera was pointed to the oscilloscope screen and transmitted the image to the video interface/monitor unit located outside the MRI room. The video interface unit was connected to a color LCD projector, located near the scanner inside the MRI room, by a long fiber-optic cable. The output of the color LCD projector was directed to a pair of adjustable biocular glasses via a fiber-optic guide. The glasses were fixed to the top window of the MRI head coil, directly above the subject’s eyes. Through the glasses, the subject, lying in the MRI chamber, could clearly see the oscilloscope screen. During the task-performance periods, the subjects exerted handgrip contractions to match the output force to the target line on the screen. They were encouraged to match the target as closely as possible during the entire contraction for the SF task or during all the contractions for the DF task.

fMRI data collection

Functional MRI images were collected on a SIEMENS VISION 1.5 T system using a circularly polarized head coil and an interleaved multislice gradient echo EPI pulse sequence (TR/TE = 115/22 ms, flip angle = 90°). The subject was positioned in the MRI chamber (supine) and was told to remain as still as possible. The head was stabilized by padded restraints and by taping the forehead to the frame of the head coil. Both T1-weighted anatomic images and functional images were collected in the same transverse planes. Each brain volume consisted of 20 slices (6-mm slice thickness) that covered the entire cerebrum and the cerebellum (the collection of 1 brain volume is referred to as 1 scan hereafter). The field of view was 256 × 256 mm. The spatial resolution was 2 × 2 mm for the fMRI images and 1 × 1 mm for the T1-weighted images.

During each experiment, the T1-weighted anatomical images were collected first. The functional brain images were then collected during rest or baseline condition (off) and during task performance (on; see Fig. 1 for the paradigms of the fMRI experiments). In both the SF and DF experiments, the off images included 12 continuous scans, during which subjects rested and watched the oscilloscope screen via the visual feedback system. On the screen, the target force was displayed as a static line. Before the off image collection, a “rest” audio signal was given to the subject (via the intercom system) as a prewarning.

The acquisition of on images began with a “start” command from the experimenter at which time the subject initiated the handgrip task. Roughly 5 s after the contraction began (due to the delay of the imaging system preparation), the fMRI pulse sequence was executed. For the SF task, 92 continuous scans of on images were collected while the subject continuously matched the target with the exerted force (Fig. 1A). For the DF task, subjects performed the contractions following a ~2-s-on/1-s-off pattern (Fig. 2A). Visual feedback of the performance was provided on the oscilloscope. Subjects had been trained to perform the DF task before the experiments and had acquired a good sense of timing of the pattern. The on images for the DF task were collected periodically (Fig. 1B). Each set of on images consisted of 12 continuous fMRI scans, and 7 sets were acquired (ON1, ON2, . . . ON7). Between each two consecutive sets, there was a waiting period of 2 min. The reason not to collect fMRI data continuously was due to the incapability of the MR system itself; the waiting periods were required for the machine to reconstruct the fMRI brain images. For both the SF and DF experiments, the first two scans in the off and on periods were excluded from the data analysis to ensure equal weighting of all fMRI data. Because each scan took 2.5 s (2.3 s for the execution of the fMRI pulse sequence plus a 0.2-s gap between any 2 adjacent executions), the off periods were 25 s (excluding the unused 1st 2 scans) and the on period for the SF task lasted 225 s. For the DF task, each of the 7 on periods lasted 25 s, and the entire task lasted ~960 s. On average, each subject performed 319 ± 28 (mean ± SD) DF handgrip contractions.

It is worth noting that there was a time delay from the start of the handgrip contraction to the beginning of the first useful fMRI data set (the 3rd scan of the on period). This period lasted ~10 s, including ~5 s of the prefMRI handgrip and the time for the first two fMRI scans (5 s) that were discarded. It has been reported that during the beginning 10 s or so of a functional task, the fMRI signal, i.e., the measured blood-oxygen-level-dependent (BOLD) effect, may not have reached its stable level (Duong et al. 2000; Logothetis et al. 2001). Therefore, the exclusion of this period ensured that our fMRI data were immune from the BOLD-induced signal instability during the initial phase of the motor task.

In separate sessions, subjects performed two types of control fMRI experiments, during which they simply watched the screen while the whole body rested (rest controls). The first type was designed to mimic the SF fatigue experiment; thus 12 fMRI brain scans were collected as off images, 92 scans were collected continuously as on images. The second type was designed as a control for the DF fatigue experiment; thus after acquiring 12 off scans, 7 sets of fMRI scans were collected periodically with temporal gaps of 2 min in between, and each set consisted of 12 scans as on images. The first two scans in each off of on period were excluded from the data analysis for the same reason mentioned in the preceding text.

Force and EMG data analysis

EMG signals during the SF fMRI experiment were measured in the central (~120 ms) portion of each 200-ms period between consecutive fMRI scans (Fig. 2C). Within an fMRI scan, the EMG signals were not readable due to high-voltage noise created by running the image acquisition pulse sequences (dark blocks in Fig. 2B). However, these short-duration EMG signals were essentially the same as the continuous signal recordings lasting for several seconds obtained either outside the scanning room or inside the scanner without applying the image acquisition pulse sequences (Dai et al. 2001). The EMG
signals were segmented, baseline corrected, rectified, and then averaged over each 25-s period. For the force data, the measured voltage signals were first converted to force (N) using the calibration equation determined previously. This relationship was derived by a quadratic fit rather than a simple linear fit that improved the accuracy of force measurement (Liu et al. 2002b). The force data were segmented and averaged in the same manner as the EMG data (in Fig. 3A, each data point represents an average of 25 s of force data). The analyzed force and EMG data were then normalized to the corresponding initial MVC values. Finally, the normalized data were averaged over the eight subjects who were used in the fMRI data analysis (see fMRI data analysis) with standard errors (SE) calculated.

For the DF fMRI experiment, however, only those gaps occurring within handgrip contractions were selected (for example, in Fig. 2, A and B, the selected gaps are indicated, ). No gaps occurring during ascending or descending phases of the dynamic forces were included for the EMG data analysis because EMG signals were considered nonstable when the forces were rising or falling. The middle 120-ms portions of the EMG signals in the selected gaps were segmented, baseline corrected, rectified, and then averaged over each of the 7 ON periods, respectively. (On average, 4 ± 1 gaps were selected during each ON period.) The averaged EMG signals in each ON period were normalized to the initial MVC value and averaged over the subjects. The force data during the same time periods for the EMG measurement were segmented, averaged over each ON period, normalized, and averaged over the subjects. For the EMG signals that were collected in the non-MRI environment, the data from each muscle were baseline corrected, rectified, and averaged over each 25-s period in the SF experiments and each 200 s (40 contractions) period in the DF experiments. (Note that EMG data collected in the non-MRI environment were all usable and thus were not subject to selection and segmentation.) The handgrip force data were averaged over the same periods. They were then normalized to the corresponding MVC values. The normalized EMG and force values were averaged over the eight subjects with SE values calculated.

fMRI data analysis

The fMRI data analysis was performed using the MEDx 3.2 software package (Sensor Systems, Sterling, VA). Before applying statistical analysis, several preprocessing approaches were performed. First, head motion was detected relative to the images of the third OFF scan (the reference scan for head motion detection/correction and image registration) in each subject. In 4 of the 12 subjects, the head motion exceeded 2 mm (the size of a pixel in fMRI images); the data from these four subjects were excluded from further analysis because data with such magnitude of head motion generally carry significant noise and are difficult to correct. The data for the remaining eight subjects were motion corrected using the automated image registration (AIR) algorithm (Woods et al. 1992, 1993) programmed in the MEDx software. All OFF and ON scans in a given experiment were corrected according to (i.e., registered to) the reference scan (the 3rd OFF scan) of the same experiment. Head motion in the eight subjects was reduced significantly after the motion correction (on average, the motion was 0.92 ± 0.38 mm before motion correction and was reduced to 0.34 ± 0.17 mm after correction for the SF experiment. For the DF experiment, the motion was 1.39 ± 0.41 mm before correction and 0.54 ± 0.27 mm after correction). Normalization of image inten-

![Figure 3](http://jn.physiology.org/)

**FIG. 3.** Force and EMG signals during the static force (SF) handgrip fatigue experiment. All force and EMG data were normalized to the maximal voluntary contraction (MVC) values in each subject, and averaged over the eight subjects. A: handgrip force measured in the SF experiment. B: EMG signals measured in the SF experiment. The muscles that were measured included flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP), and extensor digitorum (including the extensor indicis, ED) of the right arm and FDS of the left arm. C: handgrip force measured in the control experiment in a laboratory environment without influences of magnetic fields of an MRI scanner. Data from FDS, FDP, ED, first dorsal interosseus (FDI), biceps brachii (BB), deltoid (DT), and triceps brachii (TB) of the right limb are shown in C, and data from FDS, ED, and BB of the left arm are shown in D. *, significant increase (P < 0.05) compared with the 1st data point.
sity was performed to remove fMRI signal shifts over an extended experimental period (Arndt et al. 1996). The data were then smoothed spatially with a Gaussian filter (FWHM = 4 × 4 × 6 mm) (Poline and Mazoyer 1994a,b; Siegmund and Worsley 1995). A matched bandpass temporal filter was used to remove low-frequency drifts and high-frequency fluctuations in the signals (Bannister et al. 2000; Friston et al. 2000).

Student’s t-test were applied to detect fMRI signal changes. For the SF task, each 10 (1st 10 ON scans, 2nd 10 ON scans, ..., 9th 10 ON scans) of the 90 ON scans were compared with the corresponding 10 OFF scans in the same session. For the DF task, each 10 ON scans of the seven sets of ON scans (1st 10 ON, 2nd 10 ON scans, ..., 7th 10 ON scans) were compared with the corresponding 10 OFF scans in the same session of the same subject. Therefore nine data points were obtained for the SF experiment and seven for the DF experiment (the time of each data point was chosen as the middle point of the corresponding ON period). The comparisons were made on a pixel-to-pixel basis between the ON and OFF images. A Z-score map representing fMRI-measured brain activation was generated for each ON-to-OFF comparison. These maps were of the same size as the fMRI brain images (128 × 128), and each pixel of them was assigned the z value from the t-test. Cluster detection (z ≥ 3.0, P ≤ 0.0013) was then performed on the Z-score maps to improve the reliability of true brain activation (Friston et al. 1994). Pixels that reached or exceeded the threshold (z ≥ 3.0, P ≤ 0.0013) were considered to be “activated” (i.e., a significant signal increase during task performance over the rest period) (Liu et al. 2002a).

The reference fMRI brain volume (the 3rd scan in the OFF images) was registered to the T1-weighted anatomical brain volume in each experimental session in each subject using the program in MEDx. The obtained registration transforms were applied to the Z-score maps in the same session to register these maps to the same space as the T1-weighted images. Finally, the Z-score maps (shown as color points in Fig. 5) were overlaid onto the corresponding T1-weighted anatomical images of the same subject for identification of the cortical regions.

Brain activation was quantified by calculating the number of activated pixels (AP) in each Z-score map for the entire brain and for several cortical regions of interest (ROIs). The individual cortical fields being analyzed included: primary motor cortex (MI), primary sensory cortex (SI), supplementary motor area (SMA), cingulate gyrus (CG), prefrontal cortex (PFC), and cerebellum (CBL). For the MI and SI, brain activation was measured from the two hemispheres separately (MI_L: left MI; MI_R: right MI; SI_L: left SI; SI_R: right SI). For the other cortical regions, activation was measured bilaterally. The ROIs were circled manually in the T1-weighted anatomical images using the graphic tools in the MEDx software package. The definitions of the ROIs were based on brain atlas textbooks and an MRI brain atlas. Experienced neurologists at the Cleveland Clinic were consulted to confirm the identified ROIs (see Acknowledgments). These procedures were described in detail in a previous publication (Liu et al. 2002a). Average and SE of the number of AP over the eight subjects were calculated in each ROI.

Data collected in the two long-rest control experiments were analyzed in a similar manner, and the number of AP was calculated for the entire brain. For the long rest associated with the DF task, the AP was also determined in the ML_L and SI_L. Average and SE of the number of AP over the eight subjects were calculated.

Statistical analysis

Force, EMG, and fMRI AP values during the course of each fatigue task were compared with the values of the first data point using paired t-test. Pearson correlation analysis was employed to determine the relationship between changes of the brain (fMRI) and muscle (EMG) signals during the course of the fatigue process. Significance level was determined at P ≤ 0.05.

RESULTS

Force and EMG

The force and EMG results for the SF task were plotted in Fig. 3. Force was maintained at 30% MVC level almost unchanged (from ~32% MVC level at the beginning of the contraction to ~30% at the end of the task, which lasted 225 s; Fig. 3A). Surface EMG signals from the two finger flexors (FDS and FDP) of the right arm increased almost linearly from ~30 to ~35% MVC values at time t = 12.5 s to ~50% at t = 212.5 s, where t is the average time for any single data point (Fig. 3B). The last three data points for the FDP and the last three plus the mid points of the FDS EMG increased significantly (P < 0.05) compared with the first data point. The increase in the EMG signals in the prime movers of handgrip indicated that subjects had to increase their effort to maintain the same force, which was an indication of fatigue. The antagonist muscle (ED) showed a slight increase in activity from ~17 to ~22% MVC level. The activities in the FDS of the left arm remained low and showed little change throughout the experiment, indicating no significant involvement of the muscle of the left limb (Fig. 3B).

Figure 4 shows force and EMG results for the DF task. Subjects overshot the target at the beginning of the experiment (~33% MVC) but had difficulties to reach the target near the end of the experiment (~27% MVC) even with the maximal effort. The force at the end was significantly lower (P < 0.05) than the one at the beginning (Fig. 4A). The EMG signals from the FDS increased almost linearly from ~29% MVC level at the beginning of the experiment (t = 17 s) to ~55% at t = 656 s (P < 0.05) and then ceased the rise of its value from this time point (Fig. 4B). The EMG signals from the FDP changed from ~27% at t = 17 s to ~34% at t = 500 s, then decreased (P < 0.05) to ~17% at t = 942 s. The decrease in the FDP EMG and plateau of the FDS EMG signals plus the decline in force indicated that severe fatigue had occurred at the later stages of the performance. The increase in EMG activities was driven by increased voluntary effort to reach the same force; the decrease represented a decline in motor unit activity despite the subjects’ near-maximal or maximal effort during the late period of the experiment. Note that the FDP EMG decrease correlated (r² = 0.93, P < 0.05) with the faster decline in force (from ~t = 500 s, Fig. 4A). The antagonist muscle (ED) followed a similar pattern of activation of the FDS and FDP muscles. The change of the ED activity was more dramatic than that during the SF task. The EMG signals from FDS of the nonperforming (left) arm was low and changed little during the course of the task (Fig. 4B).

EMG of nonprime movers

The EMG signals measured in the non-MRI environment are shown in Fig. 3 (C and D) for the SF task and Fig. 4 (C and D) for the DF task. The results for the handgrip force and EMG of the FDS, FDP, and ED of the right arm during both the SF and DF tasks were similar to the corresponding data measured during the fMRI experiments (Figs. 3C and 4C). The EMG signals from the BB, DT, and TB of the right arm remained low and showed no apparent changes (Figs. 3C and 4C). The signals from the FDI of the right hand increased from ~7 to near 15% maximal level (P < 0.05)
during the SF task (Fig. 3C) and remained relatively stable around 20% level with some fluctuations during the DF task (Fig. 4C). Because the FDI is a synergist for index finger flexion, the changes in its activity reflect its participation and modulation during the fatigue tasks. The EMG data of the FDS, ED, and BB muscles of the left arm remained very low and did not change significantly (Figs. 3D and 4D), indicating that these muscles were not noticeably activated and fatigue had little effect on the activation levels of these muscles. The EMG data from these muscles suggest that the subsequently reported fMRI signal changes during the fatigue tasks had little influence from the nonprime movers.

**fMRI signals**

In Fig. 5, fMRI results of a subject on two sample slices are shown. Images in A represent results from the SF experiment, and those in B depict results from the DF experiment. These images demonstrate examples of the pattern of fMRI signal changes in the primary motor and sensory cortices. The activation patterns observed in these images were similar to the group data shown in Figs. 6 and 7.

The fMRI-measured cortical activities of the group during the SF task were plotted in Fig. 6. The number of activated pixels (AP) in the entire brain (Fig. 6A) increased from 1,194 ± 248 at \( t = 12.5 \) s to 3,319 ± 426 at \( t = 137.5 \) s and to 3,531 ± 439 at \( t = 212.5 \) s, representing a high rate of increase during the first 150-s performance and a lower rate of increase during the last 75-s performance. The AP number for the last five data points was significantly greater \((P < 0.05)\) than that for the first one. Because a pixel represents a unit brain volume of \( 2 \times 2 \times 6 \) mm (slice thickness) = \( 24 \) mm\(^3\), the activated brain volume increased from \( 28.66 \pm 5.95 \) cm\(^3\) at \( t = 12.5 \) s to \( 79.66 \pm 10.22 \) cm\(^3\) at \( t = 137.5 \) s and to \( 84.74 \pm 10.54 \) cm\(^3\) at \( t = 212.5 \) s.

The number of AP in the primary motor and sensory cortices contralateral to the performing hand (MI_L and SI_L, Fig. 6B) increased from very small \((
\) at the beginning of the contraction to substantially large \((\sim 150)\) at \( \sim t = 150 \) s \((137.5 \sim 162.5 \) s). The AP number then plateaued or showed a trend to decline from \( \sim t = 137.5 \) s. The activation changes in a majority of the data points in the motor cortex and the sensory cortex were significant \((P < 0.05)\) and paralleled each other in both the hemispheres. The activation sizes in the ipsilateral motor and sensory cortices (right hemisphere), although significantly lower than that of the contralateral side, also increased slowly and then remained at a relatively stable level during the course of the contraction. These signals were not associated with left hand/arm muscle activities, which were not changed in the control experiments (Fig. 3, B, D and D). The most likely explanation is that the ipsilateral sensorimotor areas were more involved in the controlling process during the later stages of the motor task, perhaps to reinforce the descending command as fatigue set in.
The number of AP in the secondary motor and association cortices (SMA, PFC, and CG) showed a trend of gradual increases during the early period and then reduced the rate of increase (PFC and SMA) or remained at a stable level (CG) at the later stage of the experiment (Fig. 6C). The number of AP in the CBL increased almost linearly throughout the course of the task performance. A number of late AP measurements for the PFC, SMA, and CBL were significantly greater ($P < 0.05$) than the first AP measurement (Fig. 6C).

The results of Pearson correlation between the fMRI and EMG signals are listed in Table 1. The figures in parentheses are $r^2$ values. The correlation was significant for all pairs that could be analyzed for the SF task. It is worth noting that all the measured cortical regions were significantly correlated with the ED muscle, antagonist of the finger flexor muscles, suggesting perhaps that the antagonist muscle was also constantly modulated by the cortical control centers.

The AP number may be affected by subjects' attempts to bring the force back on target if off-the-target errors were...
FIG. 7. fMRI results in the DF handgrip fatigue experiment. The results were averaged over the 8 subjects. A: number of activated pixels in the whole brain. Both the DF results (*) and long-rest data (●) are shown. B: number of activated pixels in the MI and SI cortices, contralaterally (MI_L, SI_L) and ipsilaterally (MI_R, SI_R). Note that results of the MI_L and SI_L during the long-rest experiment are also shown. C: number of activated pixels in the PFC, CG, SMA, and CBL. *, significant increase (P < 0.05) compared with the 1st data point.

TABLE 1. Results of the Pearson correlation tests between the fMRI signals and the EMG signals

<table>
<thead>
<tr>
<th>Pearson Correlation</th>
<th>Continuous Task, EMG (Right Hand)</th>
<th>Intermittent Task, EMG (Right Hand)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FDS</td>
<td>FDP</td>
</tr>
<tr>
<td>fMRI: whole brain</td>
<td>*(0.81)</td>
<td>*(0.83)</td>
</tr>
<tr>
<td>MI_L</td>
<td>*(0.62)</td>
<td>*(0.59)</td>
</tr>
<tr>
<td>MI_R</td>
<td>*(0.50)</td>
<td>*(0.58)</td>
</tr>
<tr>
<td>SI_L</td>
<td>*(0.66)</td>
<td>*(0.67)</td>
</tr>
<tr>
<td>SI_R</td>
<td>*(0.65)</td>
<td>*(0.73)</td>
</tr>
<tr>
<td>PFC</td>
<td>*(0.88)</td>
<td>*(0.75)</td>
</tr>
<tr>
<td>CG</td>
<td>*(0.54)</td>
<td>*(0.58)</td>
</tr>
<tr>
<td>SMA</td>
<td>*(0.73)</td>
<td>*(0.73)</td>
</tr>
<tr>
<td>CBL</td>
<td>*(0.72)</td>
<td>*(0.90)</td>
</tr>
</tbody>
</table>

*, the correlation was significant above the 95% confidence level; ns, indicates non-significance. The numbers in the parentheses are r² of the Pearson correlation. fMRI, functional magnetic resonance imaging; EMG, electromyogram; FDS and FDP, flexor digitorum superficialis and profundus; ED, extensor digitorum; MI_L and MI_R, primary motor cortex left and right; SI_L and SI_R, primary sensory cortex left and right; PFC, prefrontal cortex; CG, cingulate gyrus; SMA, supplementary motor area; CBL, cerebellum.
Pearson correlation between the fMRI and EMG signals for the DF task was quite different from that for the SF task. No significant correlation was found between the cortical areas and the fMRI-measured brain activation during the handgrip contractions using fMRI. The major findings were that the target force (30% MVC) was maintained at a relatively stable level (SF task) or declined slightly (DF task), but the EMG signals of the MVC) was maintained at a relatively stable level (SF task) or declined slightly (DF task), but the EMG signals of the MVC) was maintained at a relatively stable level (SF task) or declined slightly (DF task). The results, representing background fMRI signals, remained very low and varied very little during the entire experiment. These results indicate the changes in fMRI-measured brain activation during the handgrip contractions were indeed associated with muscle activities and affected by fatigue not due to shifts in fMRI signals as a function of time. (Possible signal shifts were corrected during the data-preprocessing stage, as mentioned in fMRI data analysis.)

DISCUSSION

The purpose of this study was to characterize brain activation patterns during fatigue tasks involving submaximal sustained SF and intermittent DF handgrip contractions using fMRI. The major findings were that the target force (30% MVC) was maintained at a relatively stable level (SF task) or declined slightly (DF task), but the EMG signals of the finger flexor muscles increased steadily, indicating significant muscle fatigue had developed; overall, the fMRI-measured brain activation level, similar to that of EMG, increased progressively during the course of the fatigue tasks; the fMRI signal of the contralateral primary sensorimotor areas showed an early rapid rise followed by a slower increase, and plateaued at the later stage for both tasks; the ipsilateral sensorimotor cortices displayed a steady increase in the fMRI signal for both the SF and DF tasks; and for both tasks, the PFC, CG, SMA, and CBL enlarged their activation areas during the course of the tasks with a substantially greater magnitude for the PFC during the DF task.

Force, EMG, and fatigue

Fatigue induced by submaximal sustained or intermittent muscle contractions and its effect on force and EMG signals have been studied extensively (for review, see Bigland-Ritchie 1981; Enoka and Stuart 1992). It is a common observation that when a submaximal force is sustained for a prolonged time or repetitively exerted, the EMG activities of the performing muscles increase to compensate for the loss of muscles’ ability to generate force (Bigland-Ritchie et al. 1986; Fuglevand et al. 1993, 1995; Yue et al. 1997). Thus an elevation in the level of EMG while maintaining a target force is an indication of fatigue. In this study, the finger flexor (FDS and FDP) EMG values for both tasks, on average, were at ~50% of prefatigue MVC level near the end of the tasks. However, this does not mean that the level of effort was only at 50% maximum. EMG signals typically do not go to the prefatigue MVC level even though subjects exert the maximal effort to sustain the contraction or attain the target force when extremely fatigued. In fact, maximal-effort EMG for a fatigue task involving sustaining ~30% target force could only reach 40~60% of the pre-fatigue MVC level (Fuglevand et al. 1993; Löscher et al. 1996; Yue et al. 1997). The reason is that when fatigue sets in, high-threshold motor units may cease firing (Peters and Fuglevand 1999), active motor units reduce their discharge rate (Bigland-Ritchie et al. 1983; Carpentier et al. 2001; Christova and Kossev 1998; Garland and Gossen 2002; Garland et al. 1994), and the amplitude of motor unit action potentials declines (Behm and St-Pierre 1997; Dietz 1978; Fuglevand 1995). When examining the results of the DF experiments, we noticed that both the force and EMG values began to decline at the later stage of the performance, indicating that the subjects had reached a state of exhaustion, and their efforts could not be further increased (indicated by reduction of the EMG signals and force). Because the level of EMG for the SF task was similar or only slightly lower than that for the DF task, it implies that the level of fatigue at the end of the SF task was also high, or subjects needed almost the maximal effort to sustain the target (30% MVC) force.

When performing the SF task, the FDS and FDP muscles were activated at a similar level, and the activation of both increased nearly linearly in a similar proportion throughout the contraction (Fig. 3B). However, this close relationship between the two muscles was lost during the DF tasks, in which the FDS consistently activated at a higher level than the FDP. Moreover, the FDP became fatigued much faster than the FDS. Several explanations may be provided for the differences in the activation level for the two muscles between the two tasks. One is that a static force was maintained in the SF task and that only required slow-twitch motor units in both muscles to participate in the performance at the beginning and gradually recruited progressively larger motor units into the task, leading to steady increases in EMG. When performing the DF task, however, because the task required rapid increases of force for each brief contraction, high-threshold motor units may be recruited (Bulser et al. 1993; Masakado et al. 1995), and these units fatigued much faster than the smaller units did. This may be the major reason that the EMG of both muscles plateaued and showed a sign of decreasing long before the end of the experiment (Fig. 4B). It is not clear why the FDP became fatigued so much more quickly than the FDS did. Fiber composition between the two muscles is similar (Johnson et al. 1973), which ruled out the possibility that the FDP is more fatigable than the FDS. Perhaps the active motor units (including those slow-twitch, fatigue-resistant units) discharged at higher rates during the DF contractions than the SF contraction (Masakado et al. 1995) and became fatigued faster. Possible changes in volume conductance (cross-talk) of the signal from other muscles during the course of fatigue might also have contributed to the EMG signal differences between the two muscles. It is interesting to note that the level of the antagonist (ED) activity was substantially higher during the DF than the SF tasks. This may be because the dynamic force task needed greater antagonist co-activation to maintain joint stability (review: Smith 1981), especially when fatigue became more severe (Psek and Capparelli 1993).

fMRI-measured brain activation—SF task

fMRI SIGNAL AND NEURONAL ACTIVITY. Although fMRI has been widely used in studying human brain function because of
its noninvasive feature and high spatial resolution, the relationship between its signal and cortical neuronal activity remained inconclusive until recently. Logothetis and co-workers (2001) performed sophisticated experiments that simultaneously recorded fMRI signals, single and multiple neuron spiking activities, and local field potential (LFP) in monkey visual cortex when visual stimuli were provided to the animals. The investigators provided convincing evidence that fMRI signals are strongly related to LFP arising from the input to and integrative processes within local neurons, rather than the spiking activities of output neurons. These results (Logothetis et al. 2001) imply that the fMRI data recorded from the ROI during our fatigue experiments reflect changes in LFP of postsynaptic neurons, which was a result of changing input signals (from presynaptic neurons) to and information processing within the population of postsynaptic neurons (Raichle 2001). Other studies reported a direct relationship between fMRI signals and single-cell firing rate (Heeger et al. 2000; Rees et al. 2000). Based on the results of Logothetis et al. (2001); the fMRI data may not directly suggest any alterations in cortical output to the performing muscles, but neither do they rule out the possibility that changes in LFP can lead to modifications in output signals of the postsynaptic neurons.

CONTRALATERAL PRIMARY SENSORIMOTOR (ML_L AND SI_L) ACTIVATION. With the functional images overlaid on corresponding high-resolution anatomical images, it was possible to selectively measure fMRI signals from the two areas separated by the central sulcus. The fMRI signals of the two fields coupled closely throughout the course of the task, increased during about the first 140 s and decreased steadily during about the last 80 s of the contraction. Increasing the activation areas in the MI and SI might suggest recruitment of a greater number of neurons for signal processing as more fatigue information was flowing in from the sensory system and for modifying the ongoing descending command based on the analyzed sensory information. Recent studies have reported increases in fMRI (Dai et al. 2001) and cerebral blood flow (Dettmers et al. 1995) signals with elevated voluntary effort in the sensorimotor regions.

It is not clear exactly why the signals of the MI and SI plateaued during the later stage of the performance. Dai et al. (2001) reported that when handgrip force and finger flexor muscle EMG increased from a low level ≤65% MVC, the number of AP in the contralateral MI and SI increased linearly; however, when the force was beyond the 65% level, the AP number actually decreased slightly. The authors speculated that the nervous system may not be able to recruit additional neurons in the primary sensorimotor areas at an effort level >65% MVC, but the activity level (e.g., discharge rate and/or synchronization) of the active neurons may continue to rise to drive for greater muscle output (Dai et al. 2001). This explanation may also be offered for the current fMRI results. As the effort to maintain the target force increased to a threshold level, no more neurons in the MI and SI could be brought into the action. In fact, the plateau of the number of AP may be a sign of fatigue of the sensorimotor cortex (central fatigue). A number of studies have reported “suboptimum” central drive during fatigue of muscle, indicating that the maximal central drive may decline or the drive may not be able to reach the maximal level (Gandevia 2001; Gandevia et al. 1996; Taylor et al. 2000). Motor cortical excitability assessed by transcranial magnetic stimulation became lower at the end of a fatigue contraction (Brasil-Neto et al. 1994), suggesting that cortical output neurons may have been affected by inputs from the inhibitory sources. The plateau effect in the fMRI signal in the later stage of the contraction may indicate increased inhibition from group III and IV afferents that convey information from pain and other sensory receptors. The inhibitory effects of these afferents on spinal motor neurons have been previously reported (Garland 1991; Garland and Kaufman 1995; Garland et al. 1988; Hayward et al. 1988, 1991).

IPSILATERAL PRIMARY SENSORIMOTOR (MI_R AND SI_R) ACTIVATION. The MI_R and SI_R fMRI signals increased steadily from <20 AP at the beginning of the task to >60 AP throughout the second half of the motor task (Fig. 6B). A number of studies have reported ipsilateral sensorimotor activity increases as a response to a greater voluntary effort to perform a motor task (Crone et al. 1998; Dai et al. 2001; Dettmers et al. 1995; Siemionow et al. 2002). The AP number increases in the MI_R and SI_R were not particularly related to muscle activity changes in the ipsilateral limb as the EMG data were almost at constant levels for the three ipsilateral muscles (Fig. 3D). Perhaps the ipsilateral sensorimotor cortex was increasingly involved in processing fatigue-related information and/or adjusting the descending command for the ongoing task as the muscle condition deteriorated.

PFC, CG, SMA, AND CBL AREAS. On average, these regions showed almost a linear increase in AP number throughout the course of the task. This observation is very similar to our recent finding of linear fMRI signal increases in these cortical fields as human subjects exerted handgrip force from low to high (Dai et al. 2001), which involved a progressive increase of voluntary effort similar to that for maintaining a target force for an extended period of time that causes muscle fatigue. It is not clear why the PFC, CG, SMA, and CBL all showed linear involvement in a motor task with an increasing effort or fatigue. A simple explanation may be that a segment of cells in these regions has a function similar to the function of those cells in the primary sensorimotor cortex, which respond proportionally to the level of effort or motor output. Previous studies have reported proportional increases in the activity of PFC (Dai et al. 2001), SMA (Dai et al. 2001; Dettmers et al. 1995; Smith 1979), CG, and CBM (Dai et al. 2001; Dettmers et al. 1995) in increasing muscle-output tasks. Very few previous data, however, are available to suggest how these cortical regions respond to muscle fatigue.

fMRI-measured brain activation—DF task

PRIMARY SENSORIMOTOR (ML_L, MI_R, SL_L, AND SL_R) ACTIVATION. Compared with the fMRI signals for the SF task, there were several differences in the sensorimotor signals for the DF task. One clear difference was that the discrepancy in the level of the signal between the contralateral and ipsilateral hemispheres was much smaller for the DF task. The peak AP number measured from the MI_L and SI_L for the SF task was >150, but that number for the MI_L and SI_L for the DF task was <90. It is not clear why greater signals were exhibited during the SF task. Perhaps the SF task was a sustained contraction that required continuous activation of the neurons,
which may result in a greater activation level in the sensorimotor cortex. On the other hand, intermittent contraction of the DF task with short periods of interruptions may have prevented the signal from accumulating to a higher level.

Second, the number of AP for the MI and SI in both hemispheres was about the same or differed only slightly throughout the SF contraction, but a relatively greater difference in the AP number between the MI and SI regions on either side was observed during the DF task. The SI consistently showed a larger number of AP compared with the MI on either side of the hemisphere. One explanation for the higher SI (compared with the MI) activity was that the nervous system might have relied more heavily on the sensory feedback in generating the motor command when controlling the dynamic force trials. The information of rate of force rising, relaxation, and level of force all needed to be fed back to the SI, and that might have resulted in higher levels of fMRI signals in the SI relative to the signals in the MI.

Third, on average, the changes in the AP number in the MI and SI of the two hemispheres showed more of a linear rise for the DF task than for the SF task, in which the number increased more sharply at the beginning and leveled off in the rest of the course. The linear trend during the DF task was particularly evident for the MI_R and SI_R (Fig. 7B). Finally, the numbers of AP were still rising for the MI_R and SI_R at the end of the DF task, but those for the MI_R and SI_R of the SF task had already plateaued before the task was terminated. We have no specific explanation for the high linearity of the fMRI signals in the primary sensorimotor areas and continuing rising of the signal in the MI_R and SI_R during the DF task. The observation certainly deserves further investigation. A common feature for both the SF and DF tasks was that the AP numbers in the MI_L and SI_L began to plateau toward the end of the tasks, although this trend seemed to start earlier for the SF task (compare Figs. 6B to 7B). This observation may suggest that for both tasks, neurons in the contralateral primary sensorimotor cortex were affected by inhibitory input, probably from the fatiguing muscles. It is difficult to imagine that increases in the sensory feedback could reduce signal levels in the primary sensory cortex. One possible explanation is that the inhibitory input (e.g., fatigue-induced pain) was also processed at higher cortical levels such as the cingulate and insular cortices (Craig et al. 1994, 1996) whose output may suppress the sensorimotor activities, leading to the so-called “central fatigue” (Gandevia 2001).

PFC, CG, SMA, and CBL areas. For the DF task, the fMRI signals in the CG, SMA, and CBL showed a trend of steady increase throughout the performance. Compared with the CG, SMA, and CBL, the PFC exhibited a substantially greater increase in the activation area (Fig. 7C), from ~200 AP at the beginning to near 700 AP at t = 660 s. The activation pattern in the PFC showed a substantial difference from that demonstrated in the SF task (compare Figs. 6C to 7C). It is not clear why the activation pattern in the PFC differed so much between the two tasks. This region may have different strategies in controlling sustained SF and repetitive DF tasks in general and under fatigue conditions, in particular.

A previous study (Dettmers et al. 1996) did not find significant changes in cerebral blood flow (except ipsilateral dorso-lateral prefrontal area) during a sustained Morse-key pressing task (1.5–4.5 min durations) at ~20% MVC level. The discrepancy in the findings of our study and those of Dettmers et al. (1996) may largely be explained by the higher muscle activation intensity (30 vs. 20% MVC) employed in our fatiguing tasks. Our EMG data showed clearly that subjects’ effort had increased and that muscles fatigued significantly during the tasks; whereas no EMG data were available to indicate degree of fatigue in the study of Dettmers et al. (1996).

Concluding remarks

Muscle fatigue has been studied for over a century, but little is known regarding how the CNS modulates the activities of the fatiguing muscle and/or how the fatiguing information affects the CNS activities. In this study, both the sustained SF and intermittent DF tasks indicated significant fatigue as indicated by progressive increases in the EMG signals. More fatigue occurred in the DF task, which was evidenced by a failure to reach the target force and a decline in the EMG level toward the end of the task. On average, the cortical activation pattern exhibited a progressive increase in the AP number, suggesting that the brain, similar to motoneuron pools in the spinal cord, attempted to compensate for the loss of force-generating ability of the fatiguing muscles by recruiting more cells into action. These cells may have been involved in forming stronger descending commands and/or processing the increasing sensory information from the fatiguing muscles. The primary sensorimotor areas increased the activation level during most part of the performance course but the level plateaued near the end; this signal plateau may be a sign of “central fatigue.” The ipsilateral primary sensorimotor area may also have participated in the control process, but the patterns seemed to be different between the SF and DF tasks. The PFC, CG, SMA, and CBL modulated the SF task in a linear fashion. The PFC however, showed a different activation pattern during the DF task from that during the SF task. The observation may be an indication of unique strategies for the PFC in controlling SF and DF muscle activities, especially when fatigue is present.

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