

# A Dynamic Network Involving M1-S1, SII-Insular, Medial Insular, and Cingulate Cortices Controls Muscular Activity During an Isometric Contraction Reaction Time Task

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**Abstract:** Magnetoencephalographic, electromyographic (EMG), work, and reaction time (RT) were recorded from nine subjects during visually triggered intermittent isometric contractions of the middle finger under two conditions: unloaded and loaded (30% of maximal voluntary contraction). The effect of muscle fatigue was studied over three consecutive periods under both conditions. In the loaded condition, the motor evoked field triggered by the EMG onset decreased with fatigue, whereas movement-evoked fields (MEFs) increased ( $P < 0.01$ ). Fatigue was demonstrated in the loaded condition, since (i) RT increased due to an increase in the electromechanical delay ( $P < 0.002$ ); (ii) work decreased from Periods 1 to 3 ( $P < 0.005$ ), while (iii) the myoelectric RMS amplitude of both flexor digitorum superficialis and extensor muscles increased ( $P < 0.003$ ) and (iv) during Period 3, the spectral deflection of the EMG median frequency of the FDS muscle decreased ( $P < 0.001$ ). In the unloaded condition and at the beginning of the loaded condition, a parallel network including M1-S1, posterior SII-insular, and posterior cingulate cortices accounted for the MEF activities. However, under the effect of fatigue, medial insular and posterior cingulate cortices drove this network. Moreover, changes in the location of insular and M1-S1 activations were significantly correlated with muscle fatigue (increase of RMS-EMG;  $P < 0.03$  and  $P < 0.01$ , respectively). These results demonstrate that a plastic network controls the strength of the motor command as fatigue occurs: sensory information, pain, and exhaustion act through activation of the medial insular and posterior cingulate cortices to decrease the motor command in order to preserve muscle efficiency and integrity. *Hum Brain Mapp* 30:675–688, 2009. ©2008 Wiley-Liss, Inc.

**Key words:** isometric contraction; reaction time; muscle fatigue; event-related magnetic fields; MEG; brain plasticity; M1-S1; SII-insula; medial insula; posterior cingulate cortex



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## INTRODUCTION

Fatigue is generally defined as a reduction in the neuromuscular system's capacity to generate force or to perform work [Asmussen, 1979; Bigland-Ritchie, 1981]. Two types of fatigue can be identified: peripheral (muscular) and central (cortical) [Asmussen, 1979; Bigland-Ritchie, 1981, 1986; Gandevia, 1998; Maton, 1991]. Peripheral fatigue implies that the ability of muscles to produce force is reduced, whereas central fatigue refers to the inability to fully execute voluntary muscle activation.

Peripheral and central fatigue have been studied by recording reaction time (RT) [Pääsuke et al., 1999; Yeung et al., 1999; Zhou et al., 1996], force, and electromyographic (EMG) activities during maximal voluntary contractions [Bigland-Ritchie, 1981; Gandevia, 2001; Nordlund et al., 2004], submaximal continuous contractions [Fuglevand et al., 1993; Garland et al., 1994; Löscher et al., 1996; Maton and Gamet, 1989], and intermittent isometric contractions [Bigland-Ritchie et al., 1986]. During isometric contractions, muscles undergo a continuous reduction in force-producing capability counterbalanced by a gradual recruitment of new unfatigued motor units until endurance time elapses [Bigland-Ritchie et al., 1986; Maton, 1981]. It is well known that changes in EMG signal indirectly indicate an increase in voluntary effort during a prolonged submaximal motor task [Fuglevand et al., 1993; Hagberg, 1981; Löscher et al., 1996].

Enhancement of voluntary effort during submaximal isometric contraction has been shown by data recorded from the brain [Dettmers et al., 1996; Liu et al., 2002, 2003]. More specifically, Liu et al. [2002] suggested that an early central adjustment strengthens the descending motor command in order to compensate for force loss and subsequent inhibition by sensory feedback as fatigue became more severe. Neurophysiological factors substantiate such a claim. When fatigue sets in, the cortical cell firing changes [Belhaj-Saïf et al., 1996] as well as the location of the sensorimotor cortex activation [Wannier et al., 1991]. Indeed, in monkeys, S1 neurons exhibit different properties from M1 neurons during isometric contractions since the discharge rate of S1 neurons varies with the force produced. This information is used as feedback to regulate fine-graded force prehension. Moreover, the nociceptive activity during maintained contractions is likely to have synaptic connections to a large pool of motoneurons and, as such, probably helps to synchronize the firing rate of the motor unit [Ciubotariu et al., 2004] and/or to decrease motor unit activity [Sohn et al., 2000]. Since muscle afferents provide significant information to cortical cells that are functionally linked to their target motor fibers, changes in motor cortex activity have been defined as a central sign of fatigue [Gandevia, 2001; Maton, 1991]. In this framework, central fatigue mainly depends on the subject's willpower and determination [Gandevia, 2001; Jouanin et al., 1993; Nordlund et al., 2004].

Numerous authors have studied the role played by cerebral structures during fatigue induced by maximal volun-

tary contractions. The main result was that central fatigue is expressed by a reduction in neural activation (for review, see Gandevia, 2001). Furthermore, during fatiguing sustained isometric contractions, positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) identified the activation of the primary sensory-motor cortices, supplementary motor areas, parietal area, bilateral secondary somatosensory (SII) area and the insula, anterior cingulate, basal ganglia (thalamus, globus pallidus, putamen); [Dettmers et al., 1996], and cerebellum [Liu et al., 2003]. Moreover, pain has been reported to activate different parts of the insula and cingulate region [Brooks et al., 2005; Niddam et al., 2002; Peyron et al., 2000, 2002].

However, these studies were unable to reveal the precise timing of the spatiotemporal cortical activations because of the poor time resolution of PET and fMRI methods. Therefore, in keeping with such findings, we used magnetoencephalography (MEG) to study the timing of cortical networks involved during muscle fatigue to show evidence of activation related to central fatigue, and activation dedicated to the preservation of muscle efficiency and integrity. Indeed, MEG and also EEG allow for very precise studies of the timing and localization of cortical activations occurring after finger stimulation [Baumgartner et al., 1991; Ishibashi et al., 2000; Meunier et al., 2001; Pizzella et al., 1999; Suk et al., 1991; Yang et al., 1993], finger movements with different inertial loads [Kristeva et al., 1990], hand movements whether spontaneous or triggered by responses to visual stimuli [Endo et al., 1996, 1999; Kristeva et al., 1991; Kristeva-Feige et al., 1994; Weinberg et al., 1990], or by peripheral nerve stimuli [Forss and Jousmäki, 1998; Hari and Forss, 1999]. In these studies, MEG has clearly contributed to mapping activity sources at their peak latencies with high spatiotemporal resolution. Different neuromagnetic field components accompanying a voluntary movement have been identified during RT: the readiness field, the motor field (MF), the movement-evoked field [MEF; Weinberg et al., 1990; Kristeva et al., 1991]. More recently, several MEFs (MEF I and II, 40–150 ms following EMG onset activity) have been proposed to reflect cortical sensory feedback from the periphery. By using dipole-modeling, Cheyne et al. [2006] brought new evidence that MEF I arises from locations in the postcentral gyrus consistent with activation of area 3b in the posterior wall of the central sulcus that receives afferent input from cutaneous and joint receptors (3a), whereas MEF II components are likely reflecting a secondary activation of the motor precentral gyrus. Moreover, MEF III has also been described at latencies greater than 100 ms with rather complex topography, but its generators have not yet been identified [Cheyne et al., 1997, 2006; Kristeva-Feige et al., 1994].

Further, MEG studies have demonstrated that nonfatiguing sustained isometric contractions, [Conway et al., 1995] or peripheral nerve stimulation during low-level isometric contractions [Forss and Jousmäki, 1998] facilitate the acti-

vation of sensorimotor cortices in response to sensory afferent feedback. These studies substantiate the fact that during fatiguing isometric contractions, sensory and proprioceptive feedback contributes to adjusting motor cortex activity, which in turn controls the spinal motoneuronal pool and thus optimizes motor execution [Gross et al., 2000; Salenius et al., 1997]. Classically, these afferences are studied during voluntary movements by triggering the MEFs on EMG onset or RT [RT as the sum of premotor time (PMT) and electromechanical delay (EMD); Yeung et al., 1999; Zhou et al., 1996].

Therefore, we assume that as muscles fatigue sets in, changes in the neuromagnetic field prior to the isometric contraction (i.e. during the RT) should reflect the sensorimotor cortex adaptation to sensory, proprioceptive and nociceptive feedback. These inputs should increase during fatigue and as a result could decrease or even prohibit the motor command itself.

## METHOD

### Subjects and Experimental Conditions

A group of high-performance male athletes ( $N = 9$ ), field hockey players from the “Bataillon de Joinville”—French elite sports battalion, all right-handed, well motivated to participate in this experiment (age:  $24.0 \pm 2.0$  years, weight:  $74.3 \pm 3.9$  kg, height:  $175.1 \pm 3.3$  cm) were studied. They were chosen because of their high level of arm muscle endurance, which allowed us to record a higher number of experimental trials than with sedentary people. None had a history of trauma or neuromuscular disease. The Ethics Committee of the University of Paris V (Paris-Cochin) approved this study, and subjects gave their informed consent.

The experimental design was influenced by the characteristics of the MEG signal, which requires signal averaging to extract the evoked magnetic field. Subjects were asked to perform intermittent isometric contractions as quickly as possible, after an 80-ms LED signal trigger (RT task). Intermittent isometric contractions were carried out for 3 s (between two consecutive LED signals) during a maximum of 200 successive trials, with an interstimulus interval of 8 s. Two experimental conditions were recorded: 1st unloaded and 2nd with weightlifting.

For each subject, before the beginning of the experiment, resting heart rate was recorded for 1 min. Subsequently, subjects executed during 3 s maximal voluntary isometric contractions (MVC) of the flexor digitorum superficialis (FDS) muscle of the right middle finger. Three MVCs were completed at intervals of 90 s and recorded by a strain gauge (average value of  $3.52 \pm 0.62$  kg across subjects).

The *unloaded condition* was then recorded (force level < 5% MVC) over 200 trials. After a 20-min rest period, the *loaded condition* in which subjects were asked to lift a weight corresponding to 30% of the higher value of their three MVC was recorded (see Table I). The weight, made

**TABLE I. Subject performance under the loaded condition [endurance time (ET)] and their reports at the end of the experiment**

Subject	30% MVC (kg)	Trials	ET (s)	Report
S1	0.9	133	1,064	Exhaustion
S2	0.96	158	1,264	Exhaustion
S3	0.96	196	1,568	Exhaustion
S4	1.1	200	1,600	Pain
S5	0.81	177	1,416	Pain
S6	1.05	100	800	Pain
S7	1.1	143	1,144	Exhaustion
S8	1.4	134	1,072	Pain, exhaustion
S9	1.1	200	1,600	Exhaustion

When subjects reported a more intense middle finger than forearm pain this was classified as pain (in the sense of cutaneous pain), whereas when the forearm pain was the highest this was classified as exhaustion (in the sense of muscular pain); only one subject reported the same level for both.

of amagnetic material, was set in front of the subject to provide a visual feedback of finger force and position. The task was performed either 200 times or until endurance time elapsed.

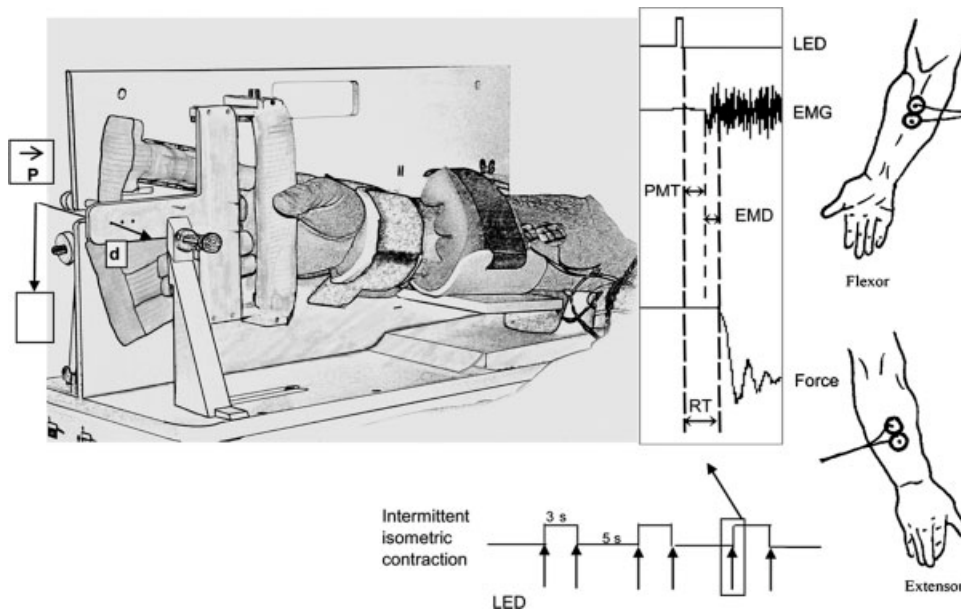
### Procedure

MEG data was collected with a whole-head 151-channel magnetometer (VMS/CTF, Canada) in a magnetically shielded room (Vacuumschmelze, Germany). Data were digitized at 625 Hz with an online 0–100 Hz band-pass. Anatomical magnetic resonance imaging (MRI) was also recorded for each subject (characteristics of the slices were  $0.9 \times 0.9$  in the axial plane and acquired every 1.3 mm).

Each subject was seated in the armchair of the MEG system, with his semipronated forearm Velcro-taped to a non-magnetic custom-designed ergometer solidly attached to the armchair. The apparatus for fixating the arm and the hand, except for the middle finger, was constructed in keeping with the finger ergograph after Mosso [Asmussen, 1979; Di Giulio et al., 2006].

To prevent inactive fingers (2nd, 4th, and 5th) from moving, the proximal and distal interphalangeal joints of the right hand and the metacarpus were taped to a plastic splint. With this device, only the metacarpophalangeal joint of the middle finger could move. It was taped to a mobile plastic sheet so that it could only move 1.5 cm, and subjects kept their thumb pronated (Fig. 1). A dacron hydraulic line transmitted the pressure variations due to finger displacement (force rise, maintained contraction, and force release) out of the shielded room to a pressure sensor. To reduce the effects of remote co-contractions on the MEG signal, subjects were attached to the armchair with Velcro bandages crossed over shoulders and chest.

Before each experimental condition started, MEG sensors had to be relocated according to the subject’s individual



**Figure 1.** From left to right: (a) nonmagnetic ergometer:  $P$  = load,  $d$  = displacement; (b) arrows: LED triggering, RT (reaction time) is the sum of the premotor time (PMT) and electromechanical delay (EMD); (c) schematic positions of the EMG electrodes.

anatomy: exact head site and orientation were measured by collecting magnetic signals from three positioning coils fixed on the nasion and both tragi. The activities of the FDS-profundus and the extensor digitorum (ED) muscles were recorded using EMG. EMG activity was recorded twice: (1) for the EMG analysis proper, at a sampling rate of 1,000 Hz by using a Biopac-systems (CEROM, France) with a 10–300 Hz bandpass. In this case EMG analysis was triggered by the LED onset. (2) EMGs were also recorded by the MEG system with a 0–100 Hz bandpass and a 625-Hz sampling rate. In order to determine the EMG onset, a trial-by-trial visual analysis of the EMG activity was done by two independent scorers for each subject and condition. These measurements were used for triggering the MF and MEFs evoked fields.

EKG was recorded via a bipolar derivation placed under the two-midclavicular lines. At the end of the experiment, subjects were asked to rate their own perceived exhaustion: pain, inability to sustain the effort, muscular fatigue, and associated pain (Table I).

**Biomechanical and Electrophysiological Data**

Heart rate (EKG), muscle activity (EMG), RT, work ( $W$ ), MF, and MEFs brain activities were recorded in unloaded and loaded conditions. Experimental conditions were divided into three periods: (1) 0–33%; (2) 33–66%, and (3) 66–100%. As a result, the loaded condition periods’ durations were related to each subject’s endurance time.

During both conditions (unloaded and loaded), EMG onset activity was defined as the beginning of the raw FDS-EMG after LED triggering.

RT was defined as the sum of PMT and EMD. PMT corresponds to the interval between LED onset and the begin-

ning of EMG activity; EMD is the interval between the beginning of EMG activity and the finger movement onset.

$W$  was computed using  $W (J) = \int Ftp$ , where  $F$  is the force,  $t = 3$  s (work time), and  $p = 3/8$  [i.e. work time, 3 s, divided by the total time, 8 s; Kahn and Monod, 1989].

In the maintained phase of the intermittent isometric contraction, root mean square (RMS) and median frequency of EMG activity were computed on a recording window of 500 ms (to avoid instability due to the movement onset) to 2.5 s after EMG onset. RMS was expressed as a percentage of the maximum RMS value obtained during MVC.

Prior to processing, after a careful visual inspection of MEG data, artifacts (blinking, ocular movement, task-unrelated EMG bursts, or abnormal slow drifts of the MEG signal) were removed. Trials where the EKG signal was of high amplitude and superimposed onto the MEG signal were also discarded. The average evoked magnetic field was then computed for each subject, for every sensor, under both conditions and for each period under analysis. Averages were triggered by the onset of EMG activity. The averaging time window went from –400 (retro averaging) to 400 ms; the baseline was computed between –400 and –200 ms. The grand average across subjects was computed and normalized by the number of trials for each subject (see Table I).

**Dipole Fit Modeling and Measurements**

For each subject, MEG-evoked fields (computed on the 151 sensors) for the different conditions and different periods were imported into the dipole-fit analyzer (CTF). MF recorded between –50 and 50 ms and MEFs between 50 and 250 ms were estimated with the standard dipole model. Each subject’s MRI was also imported into the “MRI viewer” (Dipole-Fit, CTF) for dipole modeling. Thus, each

subject's cortical anatomy was used to estimate the best fitting sphere for dipole localization procedure. For each subject, two scorers agreed on the choice in space and time of the best dipole maps around the peak or peaks of the evoked MF and MEFs. If a single dipole was able to account for 90% of these visually chosen data, then it was retained. Otherwise, one or even two supplementary localization procedures were conducted in order to add one or two dipoles, which in turn were able to explain at least 90% of the variance. During the loaded condition or during the last part of the unloaded condition, the single dipole solution only explained about 60% of the MEFs data. Thus, two or three successive dipole model-fitting procedures were used in those cases. Finally,  $x, y, z$  coordinates in the CTF system were transformed into  $x, y, z$  coordinates of the Talairach and Tournoux [1988] atlas. These data were submitted to statistical analysis and also averaged across subjects.

### Statistical Analysis

Two-way repeated measures of analysis of variances (ANOVAs) were used to analyze differences for all dependent variables (RT, PMT, EMD,  $W$ , RMS-EMG, median frequency, heart rate, MF, and MEFs) in both conditions (loaded and unloaded) for the three periods (P1: 0–33%, P2: 33–66%, P3: 66–100% of the endurance time). When necessary, a Student-Newman-Keul test was used to correct pairwise multiple comparisons (Sigmastat, SPSS Science).

A Student-Fischer  $t$ -test for paired data was used to assess dipole parameter  $x, y, z$  coordinate and strength variations. When data were missing, the Mann-Whitney Rank Sum Test was used. In order to have the same number of data points for all the subjects, regression analyses were done for 18 values extracted from P1, P2, and P3 where the P2 values were assigned to P1 or P3 as a function of the missing values of each subject.

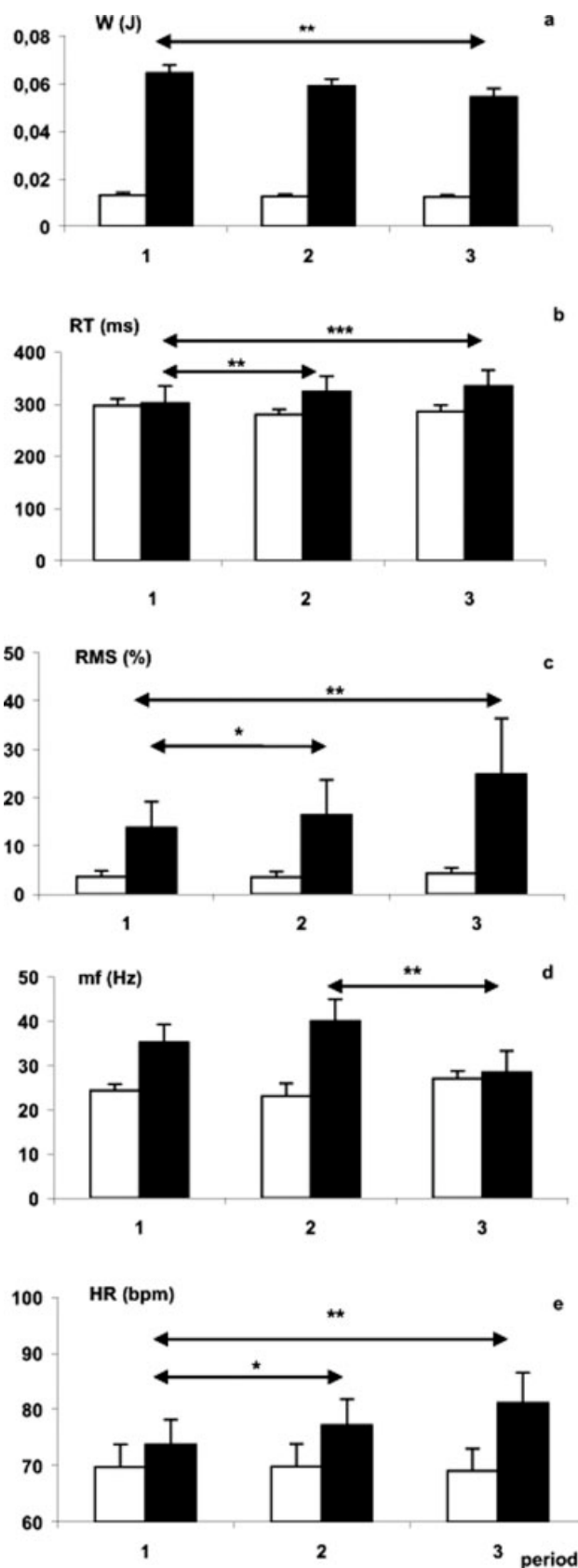
## RESULTS

### Biomechanical Data

Subjects performed 200 trials in the unloaded condition, and only  $160.1 \pm 35.5$  trials in the loaded condition (30% of the MVC). For the latter, the endurance time amounted to 21 min 20 s  $\pm$  4 min 49 s. Five subjects experienced exhaustion (i.e. inability to maintain the workload), three other subjects experienced painful sensations, and one subject felt both (Table I).

**Figure 2.**

(a) Pattern of static work ( $W$  (J)); (b) reaction time (RT (ms)); (c) RMS (%) of the flexor digitorum superficialis (FDS) EMG expressed as a percentage of the RMS-EMG of the maximal voluntary force of the FDS; (d) spectral deflection of median FDS-EMG frequency (mf (Hz)); (e) heart rate (HR (bpm)). Black bars: loaded; white bars: unloaded (\* $P < 005$ , \*\* $P < 001$ ).



Work ( $W$ ), RT, RMS-EMG, spectral mean frequency (median frequency), and heart rate (HR) changes provided evidence of muscle fatigue in the loaded condition (Fig. 2).

For  $W$ , the ANOVA showed a significant increase of  $W$  with the load ( $F_{8,1} = 27.2$ ;  $P < 0.002$ ) and a decrease with the period ( $F_{8,2} = 19.6$ ;  $P < 0.001$ ); a load  $\times$  period interaction ( $F_{8,2} = 5.23$ ;  $P < 0.02$ ) due to a decrease of  $W$  along with the periods was observed only in the loaded condition (see Fig. 2a). Since the weight to be held remained constant throughout the loaded condition, this decrease in work may only be accounted for by a reduction in the displacement of the middle finger. That is exactly what we observed when comparing displacement values between Periods 1 and 3 ( $1.38 \pm 0.13$  versus  $0.92 \pm 0.07$  cm;  $P < 0.05$ ).

RT was  $86 \pm 17$  ms higher under the loaded condition ( $F_{8,1} = 19.87$ ;  $P < 0.002$ ). No effect of the period on RT was observed for the unloaded condition; however, for the loaded condition, there was a significant difference in RT between Periods 1 and 2 and Periods 1 and 3 (all  $P < 0.05$ ), (Fig. 2b). Moreover, a load  $\times$  period interaction was significant ( $F_{8,2} = 5.47$ ;  $P < 0.02$ ) because of the absence of any period effect under the unloaded condition. Across the three periods, a significant decrease of the PMT ( $21 \pm 5$  ms) was observed ( $F_{8,1} = 8.9$ ;  $P < 0.02$ ) in the loaded condition when comparing with unloaded condition. On the contrary, the EMD increased by  $53.4 \pm 4.5$  ms in the loaded condition ( $F_{8,1} = 26.94$ ;  $P < 0.002$ ).

RMS-EMG (FDS) increased of  $27.4 \pm 4.6\%$  with load ( $F_{8,1} = 17.55$ ;  $P < 0.003$ ) with a significant period effect ( $F_{8,2} = 5.2$ ;  $P < 0.02$ ) and a load  $\times$  period interaction ( $F_{8,2} = 8.06$ ;  $P < 0.004$ ) due to the absence of any period effect under the unloaded condition (Fig. 2c). Similar results were also observed for the ED muscle.

The median frequency of FDS muscle increased of  $35.4 \pm 4$  Hz in the loaded condition ( $F_{7,1} = 13.4$ ;  $P < 0.001$ ), and there was also a period effect ( $F_{7,2} = 31.75$ ;  $P < 0.001$ ) with a load  $\times$  period interaction ( $F_{7,2} = 11.84$ ;  $P < 0.001$ ) which revealed a significant decrease in median frequency under the loaded condition for Period 3 (28.4 Hz) when compared with Period 1 (35.2 Hz) and 2 (40 Hz), (Fig. 2d). Conversely, median frequency of the ED muscle increased during Period 3 ( $P < 0.02$ ).

The RMS-EMG of the FDS muscle increased with the EMD ( $F_{16,1} = 5.604$ ,  $R = 0.52$ ;  $P < 0.03$ ). These results confirm that additional motor units must be recruited to perform the task when fatigue develops [for a review see Bigland-Ritchie, 1981]. Moreover, since the RMS-EMG of the FDS and ED muscles covaried ( $F_{17,1} = 5.34$ ,  $R = 0.5$ ;  $P < 0.003$ ), this suggests that both muscles cooperate to execute the task.

Heart rate increased with load ( $F_{8,1} = 11.66$ ;  $P < 0.01$ ) regularly during the three periods. A significant load  $\times$  period interaction ( $F_{8,2} = 7.36$ ;  $P < 0.005$ ) revealed that no heart rate variations existed in the unloaded condition (Fig. 2e). Accordingly, when fatigue increased (i) heart rate and EMD increased ( $F_{16,1} = 7.116$ ,  $R = 0.567$ ,  $P < 0.02$ )

and (ii) the work decreased whereas the RMS-EMG of the FDS muscle increased ( $F_{15,1} = 7.628$ ,  $R = -0.568$ ,  $P < 0.014$ ).

### MEG Event-Related Fields

On Figure 3 (map), grand-averaged data of the magnetic field obtained from the contralateral hemisphere including medial sensors are clearly consistent with the description of the MF peaking around the EMG onset. It displays an anterior localization and orientation, suggesting a current flow away from the anterior bank of the central sulcus, consistent with an activation of the primary sensorimotor cortex. This MF is followed by a second evoked field peaking around 100–150 ms with a posterior localization and orientation, suggesting a current flow away from the posterior bank of the central sulcus consistent with a postcentral gyrus activation which identifies the MEFs.

Subject by subject measurements of peak latencies and amplitude (Fig. 4) were done for MF on the following sensors: middle left temporal 24, 33, 34; left central 21, 41; and zenith central 01. For MEFs the sensors were left frontal 45; left temporal 12, 13, 23; left parietal 31; zenith parieto-occipital 2; right parietal 31, 32.

These measurements revealed the following:

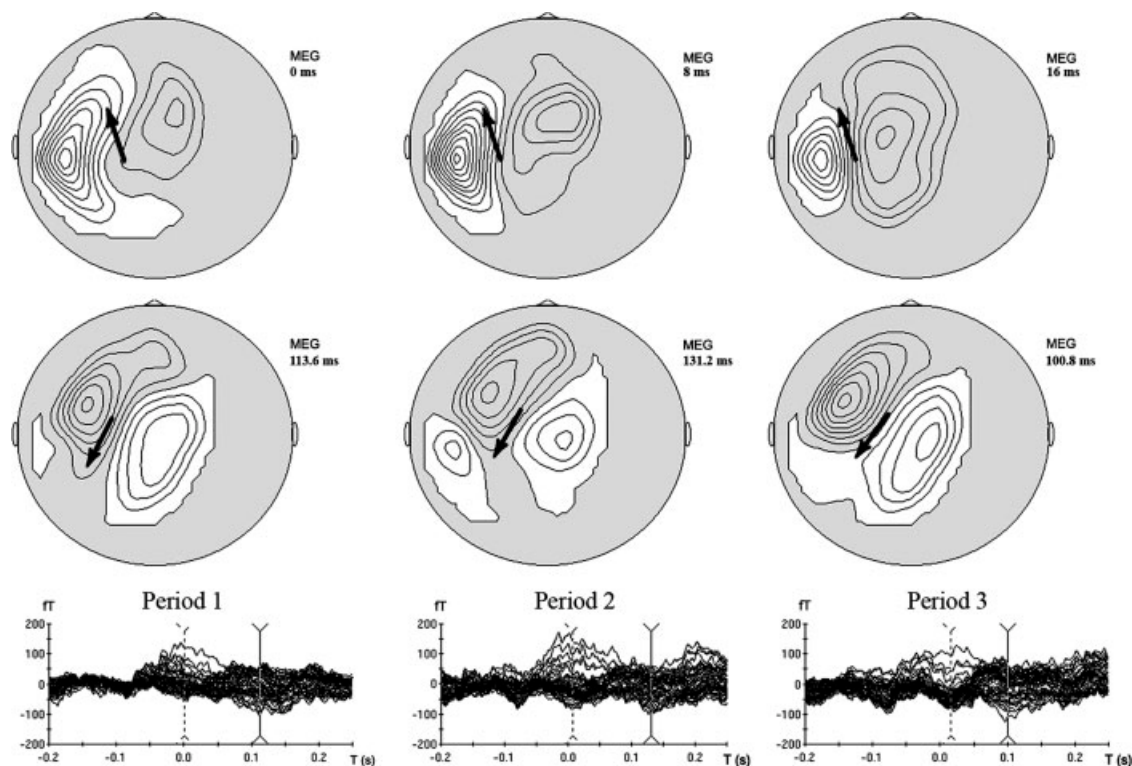
1. MF and MEFs peak latencies did not vary between unloaded and loaded conditions.
2. In the loaded condition, MF peak amplitude decreased ( $F_{8,2} = 3.7$ ;  $P < 0.05$ ) across periods ( $P < 0.02$ ). Moreover, during the 3rd period, the MF peak amplitude decreased with endurance time ( $F_{8,1} = 9.91$ ,  $R = -0.766$ ,  $P < 0.02$ ), which supports the assumption of a decrease of the motor command with fatigue.
3. Contrariwise, under the loaded condition, MEFs peak amplitude increased across periods ( $P < 0.001$ ) which support an increase of the sensory feedback with fatigue.

### Current Dipole Localization and Variations

For each subject under the unloaded and loaded conditions, the MF was well fitted by one single current dipole generally located in the vicinity of M1-S1 (see Fig. 5 and Table II) but not the MEFs which were fitted by two or even three dipoles. In general, these dipoles were located in M1-S1 and SII-insula (see Fig. 6 and Table II), but posterior cingulate activations were observed in five of the subjects who experienced muscle fatigue with exhaustion (see Table I).

During MEFs when comparing Periods 1–3, two significant shifts in dipole locations were observed in M1-S1 and SII-insula with fatigue:

1. Dipole location shifted an average of  $-12.3 \pm 1.3$  mm, from an anteroinferior position in the central sul-



**Figure 3.**

Upper row: Isocontour maps of the MF at the MEG onset (grand averaged data). Lower row: Isocontour maps of MEF at the mean peak latency (grand averaged data). Arrows represent an estimation of the main “equivalent dipole.”

cus (around 145 ms) to a postcentral gyrus position (toward 180 ms): the more posterior the location, the higher the latency ( $F_{12,1} = 5.224$ ,  $R = -0.567$ ;  $P < 0.05$ , see Table II). Moreover, this location shift correlated with signs of muscle fatigue across subjects: increase of RMS-EMG of both FDS and ED muscles ( $F_{13,1} = 17.08$ ,  $R = -0.766$ ,  $P < 0.001$  and  $F_{13,1} = 6.311$ ,  $R = -0.587$ ,  $P < 0.03$ , respectively) and increase of the EMD ( $F_{12,1} = 4.926$ ,  $R = -0.556$ ,  $P < 0.05$ ). It should also be underlined that during Period 3, the higher the median frequency shift of the FDS-EMG muscle, the higher the dipole location shift was toward S1 ( $F_{8,1} = 23.47$ ,  $R = 0.908$ ,  $P < 0.005$ ). To sum up, this shift in dipole activation from an M1 to a S1 maximum is clearly related to sensory afferences from the fatiguing muscle.

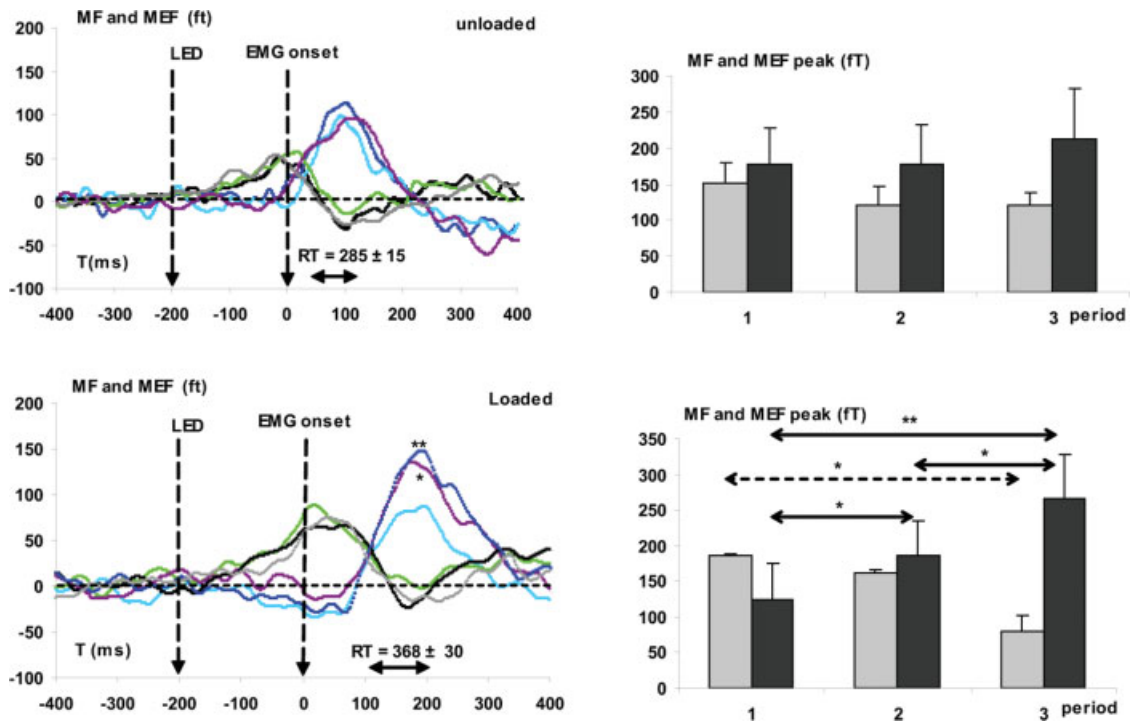
2. Dipole location shifted anteriorly  $17.9 \pm 3.9$  mm from the posterior SII-insula to the medial insula ( $P < 0.01$ ; see Table II,  $y$  coordinate). When the RMS-EMG activities of both FDS and ED muscles increased, the shift toward the medial insula position increased ( $F_{15,1} = 6.03$ ,  $R = 0.549$ ,  $P < 0.03$ ;  $F_{16,1} = 6.15$ ,  $R = 0.539$ ,  $P < 0.03$ ; respectively). It is noteworthy that during the 3rd Period, SII-insular activations were the shortest, i.e. about 35 ms before those of S1 (Table II;  $P <$

0.03). These results provide evidence that SII-posterior-insular and medial insular cortices play a primary role in the integration of sensory and nociceptive information.

## DISCUSSION

In this study, fatigue is clearly demonstrated in the loaded condition by biomechanical, behavioral, cardiovascular, and neurophysiological data. As expected, during the loaded condition, the linear increase in RT stems mainly from an increase in the EMD [Pääsuke et al., 1999; Yeung et al., 1999; Zhou et al., 1996]. Moreover, as also described by Onishi et al. [2006], during RT task, our MEG results show that MF and MEF latencies are not different between the loaded and unloaded conditions, a finding which supports that the sensorimotor cortices are activated at the same time, regardless of load and EMD. In other words, it is the EMD and the RT, which increase with fatigue.

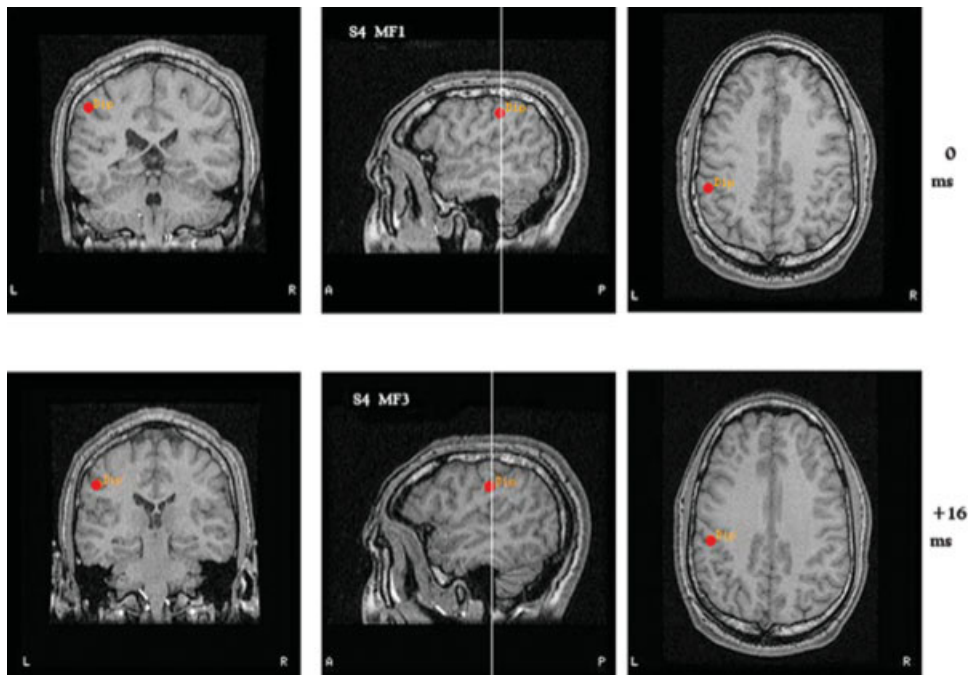
In the loaded condition, work decreased linearly from Periods 1 to 3, while the heart rate and the myoelectric RMS amplitude of both FDS and ED muscles increased. In addition, during Period 3, the spectral deflection of the



**Figure 4.**

On the left: grand average across subjects of the motor field (MF) and movement-evoked field (MEFs) during the unloaded (up) and loaded conditions (down) for the three periods. Respectively for MF and MEF: Period 1, light green and blue

lines; Period 2, gray and purple lines; Period 3, black and dark blue lines. On the right: mean amplitude of the peak across subjects. Gray bars: MF, Black bars: MEFs (\* $P < 005$ , \*\* $P < 001$ ).



**Figure 5.**

Dipole localization for the MF during the loaded condition for Subject 4. Upper MRI: The motor field during the Period 1 is labeled MF1; lower MRI: The motor field of the Period 3 is labeled MF3. The location of the MF dipole was found in the central sulcus whatever the load.



**TABLE II. Average values and standard errors across subjects of all the dipole locations found in this study during P1 and P3 periods, under the unloaded and loaded conditions**

Period	Latency (ms)	Strength (nAm)	Declination (deg)	Azimuth (deg)	x (mm)	y (mm)	z (mm)	N	Localization
MF									
Unloaded									
P1	17.2 ± 6.8	27.9 ± 5.5	72.5 ± 11.3	221.9 ± 42.3	-33.9 ± 2.5	-14.5 ± 2.1	44.1 ± 1.1	6	Central sulcus M1
P3	9.2 ± 7.3	21.9 ± 6.3	71.8 ± 6.3	154.5 ± 50.4	-36.1 ± 3.4	-18 ± 6.4	41.4 ± 5.5	6	Central sulcus M1
Loaded									
P1	4.3 ± 5.0	17.7 ± 2.1	98.5 ± 9.7	179.9 ± 40.0	-32.5 ± 2.8	-12.1 ± 2.4	45.2 ± 2.5	8	Central sulcus M1
P3	9.7 ± 5.0	31.6 ± 11.3	103.9 ± 8.3	139.1 ± 34.0	-37.5 ± 1.8	-13.1 ± 2.5	44.9 ± 2.2	6	Central sulcus M1
MEF									
Unloaded									
P1	138.3 ± 10.5	33.7 ± 3.3	93.3 ± 10.2	260.6 ± 31.5	-32.4 ± 1.9	-16.7 ± 2.9	46.6 ± 1.6	7	Central sulcus M1
P3	162.6 ± 20.4	39.5 ± 7.3	84.6 ± 5.0	189.8 ± 19.5	-33.5 ± 2.2	-17.0 ± 2.5	45.1 ± 1.9	6	Central sulcus M1
Loaded									
P1	144.7 ± 10.1	48.7 ± 12.7	91.7 ± 7.7	207.4 ± 35.1	-34.4 ± 1.5	-17.7 ± 1.2	47.7 ± 1.2	7	Central sulcus M1
P3	180.5 ± 17.0*	28.9 ± 3.8	74.2 ± 3.9	218.3 ± 23.6	-38.1 ± 1.1	-30 ± 1.3**	47.3 ± 1	7	Postcentral gyrus S1
Unloaded									
P1	162.8 ± 22.0	41.9 ± 8.6	76.7 ± 21.1	279.2 ± 27.8	-35.3 ± 2.9	-28.7 ± 1.7	15.0 ± 2.8	7	SII-posterior insula
P3	147.7 ± 11.4	64.0 ± 26.1	125.0 ± 11.6	279.0 ± 47.7	-37.1 ± 2.7	-18.8 ± 6.3	18.2 ± 3.0	6	SII-posterior insula
Loaded									
P1	153.8 ± 19.1	46.9 ± 9	74.6 ± 16.8	248.8 ± 39.2	-34.3 ± 1.7	-26.3 ± 2.9	14.9 ± 4	9	SII-posterior insula
P3	144.4 ± 14.3 <sup>§</sup>	37.3 ± 7.2	93.0 ± 13.0	255.6 ± 36.5	-36.3 ± 1.2	-8.4 ± 4.8**	17.8 ± 3.2	8	Medial insula
Unloaded									
P3	150.0 ± 28.7	49.7 ± 12	98.0 ± 12.5	187.8 ± 13.6	-6.1 ± 2.1	-30 ± 7	40.6 ± 3.5	4	Posterior cingulate
Loaded									
P1	121.0 ± 18.1	91.2 ± 20.2	88.6 ± 4.1	231.7 ± 32.3	-10.3 ± 1.9	-32.6 ± 7.7	25.7 ± 5.4	5	Posterior cingulate
P3	136.0 ± 19.8 <sup>§§</sup>	93.3 ± 17	89.0 ± 3.5	200.7 ± 42.2	-7.8 ± 3	-26.1 ± 8.6	34 ± 5.9	6	Posterior cingulate

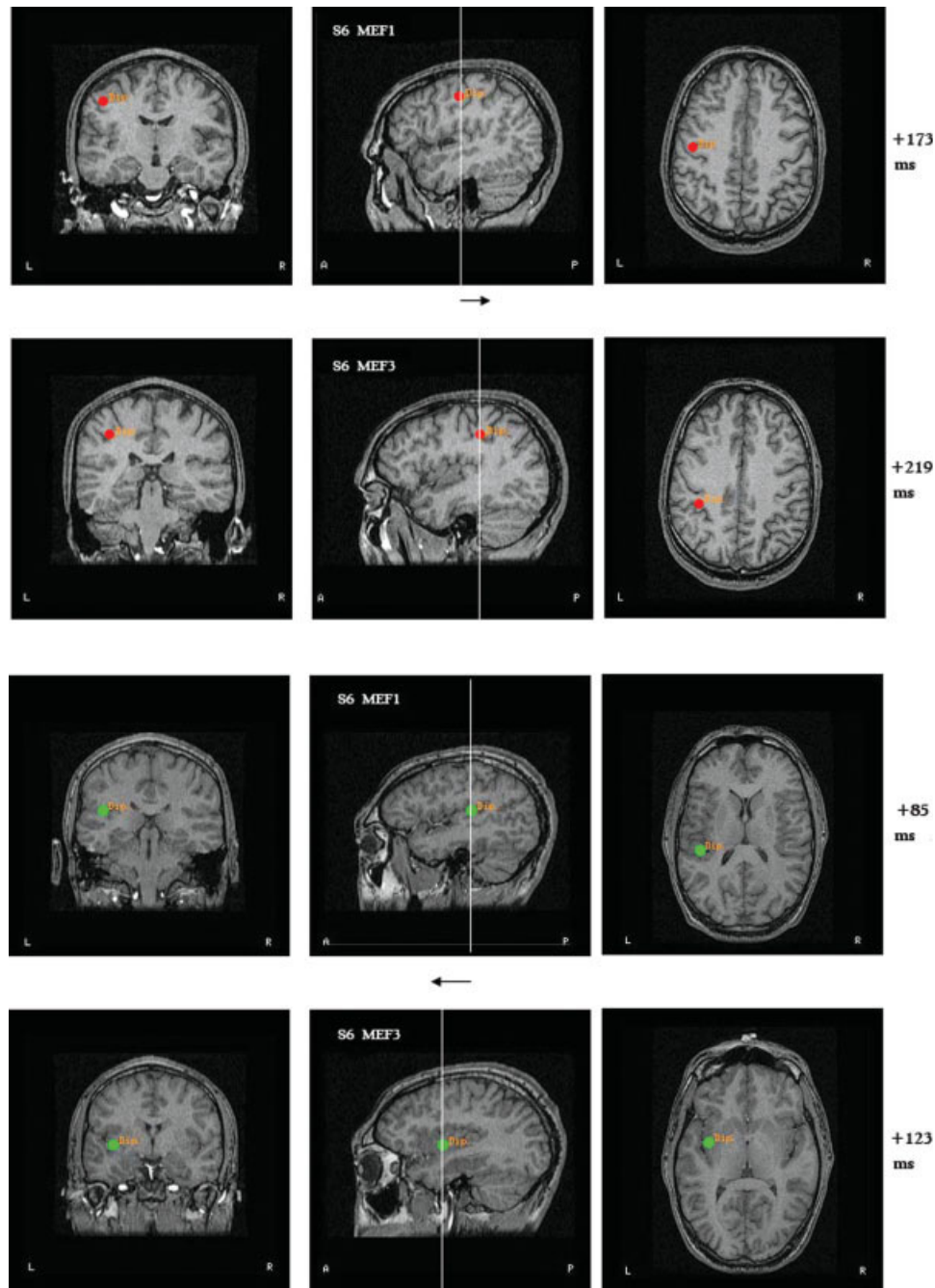
Significant variations levels are noted as follows: (1) \* $P < 0.05$  and \*\* $P < 0.01$  for the P3 versus P1 latency and  $y$  coordinate comparisons; (2) <sup>§</sup> $P < 0.05$  and <sup>§§</sup> $P < 0.01$  for latencies comparisons during the Period 3 of the medial-insular or the posterior cingulate area versus the postcentral gyrus (S1).

EMG median frequency of FDS muscle shifted to a lower frequency. These results are well-recognized signs of fatigue [Gerdle and Karlsson, 1994; Hagberg, 1981; Kleine et al., 2001; Löscher et al., 1996; Mannion and Dolan, 1996]. Further, it is noteworthy that, in the loaded condition, RMS-EMGs of the FDS and ED muscles increase even though the work decreases, a finding which substantiates the view that subjects produced a voluntary effort to execute the task until the endurance time elapsed [Gandevia, 2001; Jouanin et al., 1993]. To sum up, with fatigue the reduced motor drive very likely leads to a decrease in motor units firing rate or recruitment while the motoneurons discharge decreased. Moreover the increase in RMS at the end of the task that is lower than the RMS of the maximal voluntary contraction supports a decrease in motor drive with central fatigue [Löscher et al., 1996].

Neuroimaging studies [Dai et al., 2001; Dettmers et al., 1995] have reported a proportional relationship between cortical signals and exerted force, indicating that brain signals are positively correlated to voluntary effort, as a higher level of effort is required for exerting greater muscle force. However, during muscle fatigue, a number of studies have also reported “suboptimal” central drive, indicating that the maximal central drive may decline, may not be able to reach the maximal level [Gandevia, 1998, 2001; Taylor et al., 2000] or plateaued [Liu et al.,

2003]. Moreover, it has also been shown that motor cortical excitability assessed by transcranial magnetic stimulation was lower at the end of fatiguing contractions, suggesting that cortical output neurons may have been affected by inputs from inhibitory sources [Brasil-Neto et al., 1994; Gandevia, 2001]. Our MEG data contribute to clarify when and why different intensities of the central drive may be observed. Indeed, we found that MF decreases whereas MEFs increase during the task (Table II). Thus, if the time window of measured activations does not allow separating MF from MEFs activities (which is the case with PET and fMRI studies), activations can remain stable, and increase or decrease with no clear relationships with the fatigue induced by the task since MF and MEFs activations are pooled.

In our results, MEFs are not only explained by M1-S1 activations [Cheyne et al., 2006; Kristeva-Feige et al., 1994] but also by activation of SII-insula, medial insula, and posterior cingulate. Indeed, sensory afferent feedbacks in S1 and SII-insula and medial insula were demonstrated in humans during cutaneous pain [Bingel et al., 2004; Garcia-Larea et al., 2003; Howland et al., 1995; Kakigi et al., 2004; Oshiro et al., 1998; Qiu et al., 2004; Tran et al., 2002; Youell et al., 2004], muscle pain [Ferretti et al., 2003; Schreckenberger et al., 2005; Svensson et al., 1997], and with mechanical [Gelnar et al., 1999; Ringler et al., 2003] or electrical



**Figure 6.**

Examples of dipole shifts for the Subject 6 during the MEF. The two upper rows show the shift of the dipole location from the precentral to the postcentral gyrus. The two lower rows show the dipole shift from the posterior SII-insula (in Period I, labeled here MEF1) to the medial insula (in Period 3: MEF3). Note that for this subject SII-insula and medial insula activations precede MI and SI activations by about 100 ms.

stimuli [Kakigi et al., 1995]. Moreover, MEFs are known to reflect afferent input to the sensorimotor area from moving muscles (muscle spindles or Golgi tendon organs) and cutaneous input [Cheyne et al., 1997; Hari and Forss, 1999;

Weinberg et al., 1990]. More precisely, muscles spindle responses are activated 50–100 ms after EMG onset during isometric contractions [Vallbo, 1971]. These latencies are in the same latency range as MEF1 [Cheyne et al., 2006],

which supports an increase in MEFs amplitude due to these afferences.

In our study the dipole shift from M1 to S1 during the loaded condition does covary with myoelectric signs of fatigue. It should be underlined that dipole location is at the barycenter of a complex piece of cortical surface of which the extension may approximate 1 or 2 cm<sup>2</sup>. Thus, this shift should not be interpreted as a deactivation of M1 but as a balance of activity between M1 and S1, which is centered in M1 at the beginning of the loaded condition and in S1 at the end. This further substantiates the view that muscle fatigue induces a sensory feedback in S1 (especially tactile and proprioceptive afferent input to area 3b and 3a), which in turn contributes to a decrease of motor cortex activity (in the hand region of the precentral gyrus areas 6 and 4). This interpretation is corroborated by the results of Balzamo et al. [2004] and Masakado et al. [2004], who described direct nociceptive afferences (cutaneomuscular) from the sensorimotor area (S1) to the primary motor cortex.

Indeed, we also found a shift of activation from posterior SII-insular to medial insular cortex: the higher this shift, the higher the increase of the RMS-EMG. This clearly supports a relationship between medial-insular activation and fatigue accompanied by pain and exhaustion. As also supported by our results, the electrogenesis of the MEF components should depend on sensory and nociceptive afferences projecting directly in S1 and in the caudal part of SII-retroinsular cortex [Iannetti et al., 2005; Inui et al., 2003; Mima et al., 1998, Peyron et al., 2000, 2002; Qiu et al., 2004; Tran et al., 2002]. Mechanoreceptor inputs appear to be dominant in S1 [Ringler et al., 2003], and the insula also receives inputs from several areas associated with pain processing such as SI, SII, and the anterior cingulate cortex [Niddam et al., 2002; Svensson et al., 1997]. Ferretti et al. [2003] described two SII representations: a medial one for muscle nociception and a posterior one for skin nociception. Given that, in our loaded condition, the displacement of the middle finger reduces with fatigue, skin nociceptive receptors should be less activated than muscle receptors, which could explain the shift to the medial-insula. Actually, Henderson et al. [2007] have demonstrated that posterior insula activation is observed in response to cutaneous pain, whereas muscle pain induces more anterior activation. This is also supported by our study since posterior or more medial-anterior insula activations are, respectively, observed in relation to cutaneous pain during Period 1 and mainly in relation to muscular pain during Period 3. Moreover, painful and nonpainful somesthetic representations in human insula overlap [Craig et al., 1996; Ostrowsky et al., 2002]. Neurons in the anterior insular cortex project into various limbic structures; hence, it may be argued that this region endorses a critical role inasmuch as it correlates ongoing pain with prior pain experiences and with both the motivational and affective components of pain [Brooks and Tracey, 2007; Svensson et al., 1997]. In addition, attention-related influence is

known to enhance SII responses [Mima et al., 1998], because maintaining an isometric contraction requires sustained attention to the site of stimulation [Vråna et al., 2005].

Co-contractions of other digits, hand, arm, and shoulder muscles, which occur in our study with fatigue, were most likely involved in the changes in S1 and medial-insular activities. Two studies support this assumption. Lin et al. [2000] have shown that SII responses were differently affected by isometric contractions of various body parts: SII responses were greater during the isometric contraction of the thenar muscles, and also enhanced by the contraction of the deltoid muscle. Furthermore, Forss and Jousmäki [1998] measured the somatosensory evoked field during a submaximal isometric contraction of thenar muscles. They argued that isometric contractions facilitate the activation of SII cortices to tactile stimuli, possibly by decreasing inhibition from S1 cortex. Modulation of SII-insula activity, therefore, seems to depend on the topographical proximity of contracting muscles with the stimulated body part. Indeed, our results are in accordance with Ruben et al. [2001] who described a somatotopic representation in SII within the contralateral parietal operculum. They found finger representations within the contralateral operculum, roughly halfway between the lip of the lateral sulcus and its fundus, whereas the representation site of the hallux was found more medially to this position at the fundus of the lateral sulcus near the posterior pole of the insula. Since at the end of the loaded task (P3) subjects also gripped the handrail with the hallux, this can explain a part of the observed variability in dipole locations across subjects.

In our study, the six subjects who depicted activations of the posterior cingulate cortex also experienced exhaustion (or pain and exhaustion; see Table I). The posterior part of the cingulate cortex has been shown to be a skeletomotor region [Vogt et al., 2003] also activated during pain-motor interactions [Vråna et al., 2005]. Moreover, Vogt et al. suggested that the posterior cingulate cortex could coordinate skeletomotor reflex responses. Our results support this assumption for muscular nociceptive input. Indeed, it is only during the third part of the fatiguing loaded task, but not during the unloaded condition, that posterior cingulate and medial insula activations do significantly precede S1 activation (40 ms).

To our knowledge, this MEG study provides for the first time evidence that, during MEFs, the nodes of a spatiotemporal network differently cooperate as a function of muscular fatigue. The main nodes of this network are primary motor cortex (M1), somatosensory cortex (S1), SII-posterior insular area, medial insula, and posterior cingulate cortices. The timing of activation of these nodes and the relative balance of its activities do vary with fatigue. Indeed, during unloaded or nonfatiguing periods, activations of the nodes are massively parallel. On the contrary, during fatiguing and exhausting parts of the task, activations appear to be under the control of both medial insula and

posterior cingulate cortices whose latencies of activation are shorter than those of the sensorimotor cortex. This supports that these regions are critically involved in the control of movement execution by increasing the response time (EMD) and/or inducing skeletomotor reflexes in order to preserve muscle efficiency and integrity.

Finally, these results were obtained for a homogenous group of high-performance male athletes, with a high level of endurance, who may demonstrate abilities somehow different from those that would have been observed for a more sedentary control group. Nevertheless, we think that they represent a good picture of the neural basis of central fatigue that could be challenged in future by further studies.

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