Cerebral Blood-Flow Changes Induced by Paired-Pulse Transcranial Magnetic Stimulation of the Primary Motor Cortex

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Strafella, A. P. and T. Paus. Cerebral blood-flow changes induced by paired-pulse transcranial magnetic stimulation of the primary motor cortex. *J Neurophysiol* 85: 2624–2629, 2001. Positron emission tomography (PET) was used to assess changes in regional cerebral blood flow (CBF) induced by paired-pulse transcranial magnetic stimulation (TMS) of primary motor cortex (M1). The study was performed in eight normal volunteers using two Magstim-200 stimulators linked with a Bistim module. A circular TMS coil was held in the scanner by a mechanical arm and located over the left M1. Surface electrodes were used to record motor evoked potentials (MEPs) from the contralateral first dorsal interosseous muscle (FDI). Cortical excitability was evaluated in the relaxed FDI using a paired conditioning-test stimulus paradigm with two interstimulus intervals (ISIs): 3 and 12 ms. The subjects were scanned three times during each of the following four conditions: *1*) baseline with no TMS (BASE); *2*) single-pulse TMS (TMSsing); *3*) 3-ms paired-pulse TMS (TMS3); and *4*) 12-ms paired-pulse TMS (TMS12). CBF and peak-to-peak MEP amplitudes were measured over each 60-s scanning period. To assess TMS-induced changes in CBF, a *t*-statistic map was generated by first subtracting the single-pulse TMS condition from the 3- and 12-ms paired-pulse TMS conditions and then correlating the CBF differences, respectively, with the amount of suppression and facilitation of the EMG responses. A significant positive correlation was observed between the CBF difference (TMS3-TMSsing) and the amount of suppression of EMG response, as well as between the CBF difference (TMS12-TMSsing) and the amount of facilitation of EMG response. This positive correlation was observed in the left M1, left lateral premotor cortex, and right M1 in the case of 3-ms paired-pulse TMS, but only in the left M1 in the case of 12-ms paired-pulse TMS. The above pattern of CBF response to paired-pulse TMS supports the possibility that suppression and facilitation of the EMG response are mediated by different populations of cortical interneurons.

INTRODUCTION

A subthreshold (conditioning) transcranial magnetic stimulus (TMS) over the human primary motor cortex modulates the amplitude of the motor-evoked potential (MEP) produced by a suprathreshold (test) stimulus delivered a few milliseconds later. The MEP is inhibited at conditioning-test intervals of 1–5 ms and facilitated at conditioning-test intervals of 8–20 ms (Kujirai et al. 1993; Nakamura et al. 1997; Ziemann et al. 1996). Several lines of evidence indicate that this modulation occurs in the cortex: *1*) recordings with epidural electrodes over the cervical spinal cord show that the conditioning stimulus modulates the amplitude of later indirect (I)-waves produced by the test stimulus but not that of direct (D)-waves (Nakamura et al. 1997); and *2*) the conditioning stimulus does not influence the spinal H-reflex (Kujirai et al. 1993; Ziemann et al. 1996). The early inhibition and later facilitation are thought to arise from separate pools of cortical interneurons (Ziemann et al. 1996). However, the exact neurophysiological mechanism underlying these effects remains to be elucidated. Previous studies (Bohning et al. 1999; Fox et al. 1997; Paus et al. 1997, 1998; Siebner et al. 1998, 2000) have shown that functional brain imaging can be used to measure TMS-induced changes in brain activity. The aim of the present investigation was to study with positron emission tomography (PET) cerebral blood flow (CBF) changes induced by paired-pulse TMS applied over the left primary motor cortex (M1).

METHODS

Experimental design

CBF changes were measured during single and paired-pulse TMS in eight normal volunteers. Magnetic stimuli were applied over the left M1, and electromyographic (EMG) responses were recorded from the right first dorsal interosseous (FDI) muscle. In each subject, CBF was measured during 12 60-s ^{15}O-H_2O scans acquired with the CTI/Siemens HR+ tomograph scanner. During all scans the subjects relaxed and kept their eyes closed while white noise (90-dB SPL) was played through insert earphones to mask the coil-generated clicks. Cortical excitability was tested in the relaxed FDI using a paired conditioning-test stimulus paradigm with the following two interstimulus intervals (ISIs): 3 and 12 ms. The subjects were scanned during the following four conditions: *1*) baseline with no TMS (BASE); *2*) single-pulse TMS (TMSsing); *3*) 3-ms paired-pulse TMS (TMS3); and *4*) 12-ms paired-pulse TMS (TMS12). In each subject, scanning was repeated three times for all four conditions (blocks A, B, and C). The order of conditions within each block was randomized across subjects.

Subjects

Five female and three male subjects (19–36 yr) participated in the study after giving written informed consent. All subjects but one were right-handed. The experiments were approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital.

Transcranial magnetic stimulation

TMS was carried out with two Magstim-200 magnetic stimulators connected by a bistim module (Magstim, Spring Gardens,

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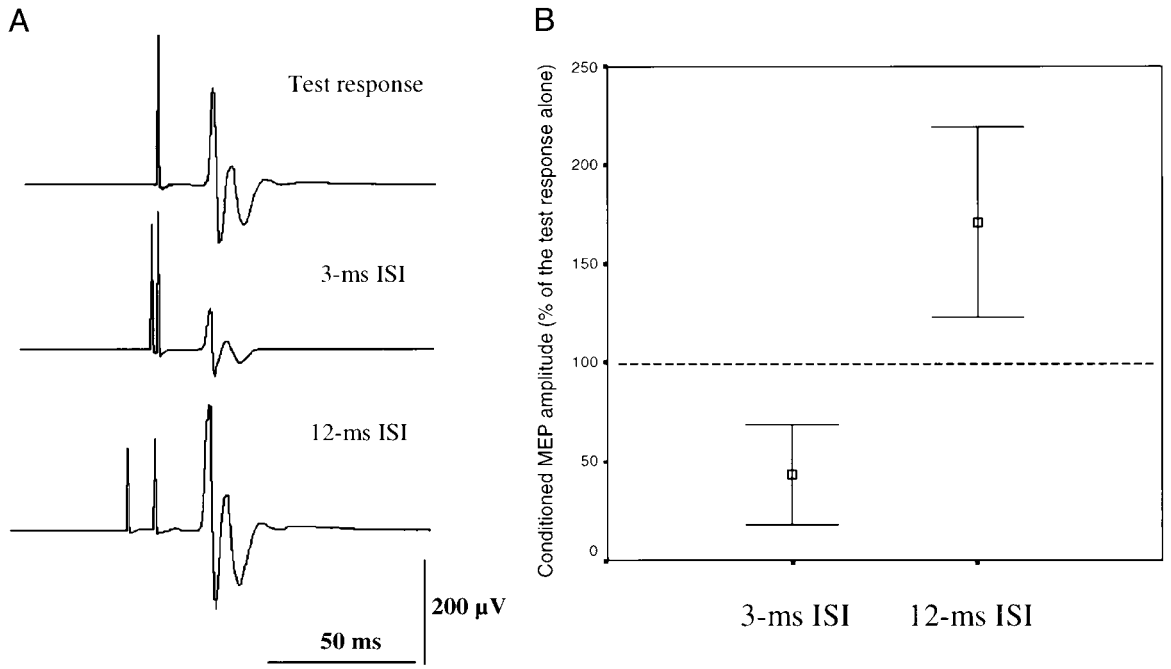


FIG. 1. Electromyographic (EMG) responses to paired-pulse transcranial magnetic stimulation (TMS) in relaxed right 1st dorsal interosseous (FDI). *A*: EMG responses in the FDI to test stimulus alone and when conditioned by a subthreshold stimulus given 3 and 12 ms earlier. *B*: the effect of paired-pulse stimulation on EMG responses for all eight subjects (mean ± SD). The conditioning stimulus suppressed test responses at 3-ms interstimulus interval (ISI; $P < 0.01$) and enhanced them at 12-ms ISI ($P < 0.01$).

Wales, UK). This device allows delivery of two magnetic stimuli through the same coil. In this paper, stimulus intensities are expressed as a percentage of the maximum stimulator output when connected to the Bistim module. TMS was delivered through a circular coil (9-cm external diam) oriented so that the induced electric current flowed in a posterior-anterior direction over the left M1. The coil was held in the scanner in a fixed position by a mechanical arm over the area where the lowest motor threshold was obtained. MEPs were recorded from the right FDI muscle with Ag/Cl surface electrodes fixed on the skin with a belly-tendon montage. EMG signal was amplified (gain: ×10,000), filtered (10 Hz to 10 kHz band-pass), digitized at 2 kHz, displayed on the computer screen, and stored for off-line analysis. Peak-to-peak MEP amplitudes were measured automatically with the Matlab program (MathWorks). Motor threshold (MT) was determined for both relaxed (rMT) and tonically active (aMT) muscle by reducing stimulation intensity (in 1% steps) from the initial suprathreshold level. Relaxed MT was defined as the lowest stimulus intensity sufficient to elicit 5 MEPs of at least 50 μV in a series of 10 stimuli delivered with at least 5-s intervals. During the determination of aMT, subjects were instructed to maintain a steady muscle contraction of 30% of their maximum voluntary contraction (MVC). Active MT was defined as the lowest stimulus intensity sufficient to elicit an MEP of at least 50 μV averaged over 10 consecutive trials delivered with at least 5-s intervals; averaging was performed to separate these small MEPs from voluntary muscle activity. Cortical excitability was tested in the relaxed FDI using a paired conditioning-test stimulus paradigm. The effect of the first (conditioning) stimulus on the second (test) stimulus was investigated at the following ISIs: 3 and 12 ms. The intensity of the conditioning stimulus was set 5% below aMT. The second, i.e., test, stimulus, was adjusted to evoke an MEP of about 0.5 mV peak-to-peak amplitude in relaxed muscle. In each subject, 20 trials were administered (intertrial interval: 3 s) during the 60-s scan in each of three different settings: TMSsing, TMS3, and TMS12 conditions.

Positron emission tomography

PET scans during TMS stimulation were obtained with a CTI/Siemens HR+ 63-slice tomograph scanner operated in a three-dimensional (3-D) acquisition mode. The distribution of CBF was measured during a 60-s scan by means of the ^{15}O-labeled H_2O bolus method (Raichle et al. 1983). In each scan, 10 mCi of ^{15}O-labeled H_2O was injected into the left antecubital vein. The CBF images were reconstructed with a 14-mm Hanning filter, normalized for differences in global CBF, co-registered with the individual MRIs (Woods et al. 1993) and transformed into standardized stereotaxic space (Talairach and Tournoux 1988) by means of an automated feature-matching algorithm (Collins et al. 1994). To protect the photomultipliers in the PET detectors from the effects of the coil-generated magnetic field, a well-grounded cylindrical insert consisting of four layers of 0.5-mm-thick mu-metal whose outer diameter matched the inner diameter of

TABLE 1. *Brain regions with significant correlations between CBF difference and the amount of EMG suppression and facilitation*

Region (BA)	*X*	*Y*	*Z*	*t*
Paired-pulse 3-ms ISI				
Left precentral gyrus (4)	−27	−19	61	3.6
Left lateral premotor cortex (6)	−13	−2	63	3.6
Right precentral gyrus (4)	23	−23	63	3.5
Right lingual gyrus (19)	28	−52	−4	−3.9
Paired-pulse 12-ms ISI				
Left precentral gyrus (4)	−35	−16	48	3.8
Left inferior frontal gyrus (11)	−49	35	−15	3.7
Right posterior cingulate gyrus (31)	4	−62	28	−3.6
Right thalamus	7	−24	11	−3.6

CBF, cerebral blood-flow; EMG, electromyographic; (BA), Brodmann's areas; ISI, interstimulus interval.

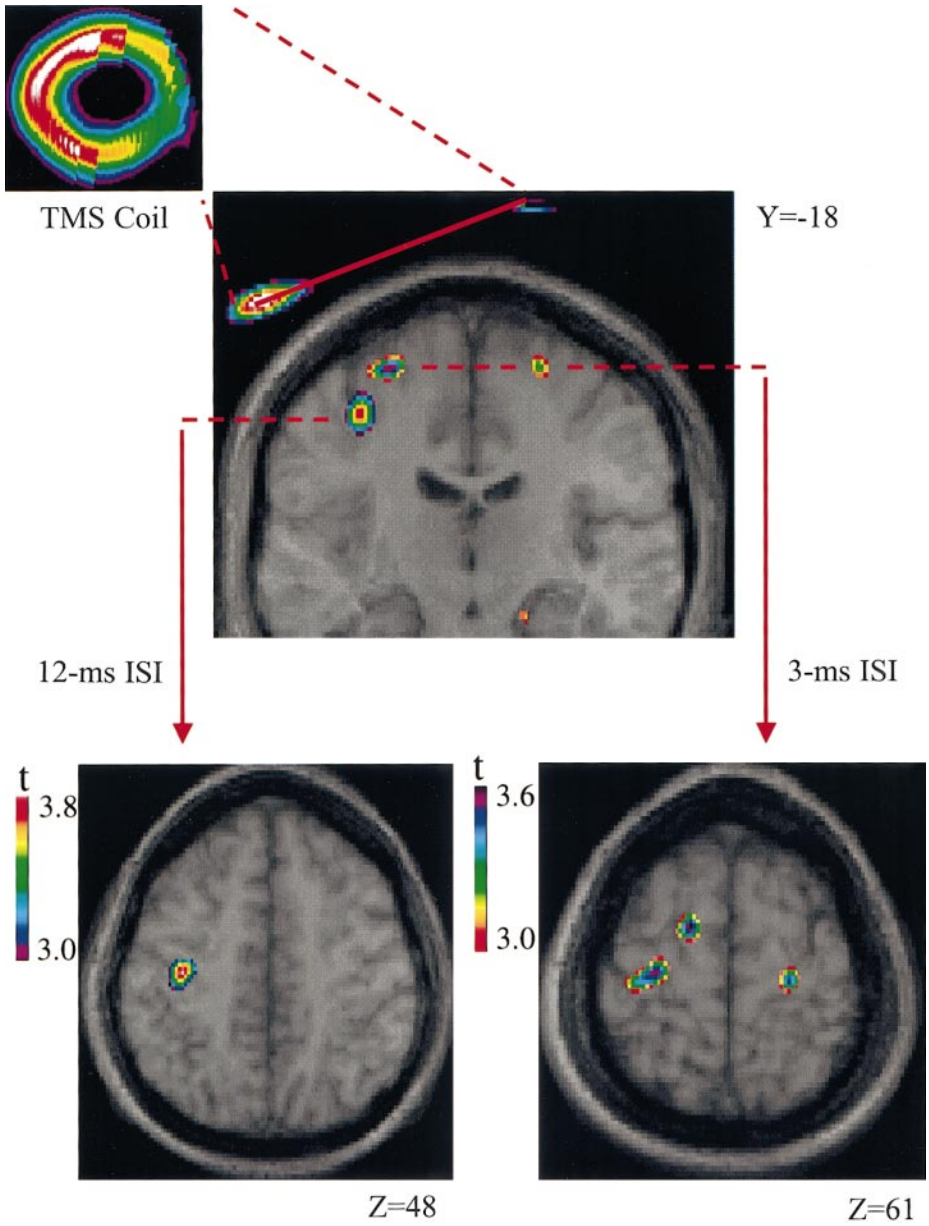


FIG. 2. The *top* of the figure shows the position of the TMS coil obtained with the transmission scan to verify the coil position relative to subject's head. The superimposed coronal section of merged positron emission tomography/magnetic resonance imaging (PET/MRI) volumes show the locations of brain regions in which cerebral blood-flow (CBF) differences co-varied significantly with the amount of EMG suppression and facilitation. The *bottom figures* show horizontal sections of 12-ms (*left*) and 3-ms (*right*) paired-pulse TMS scans.

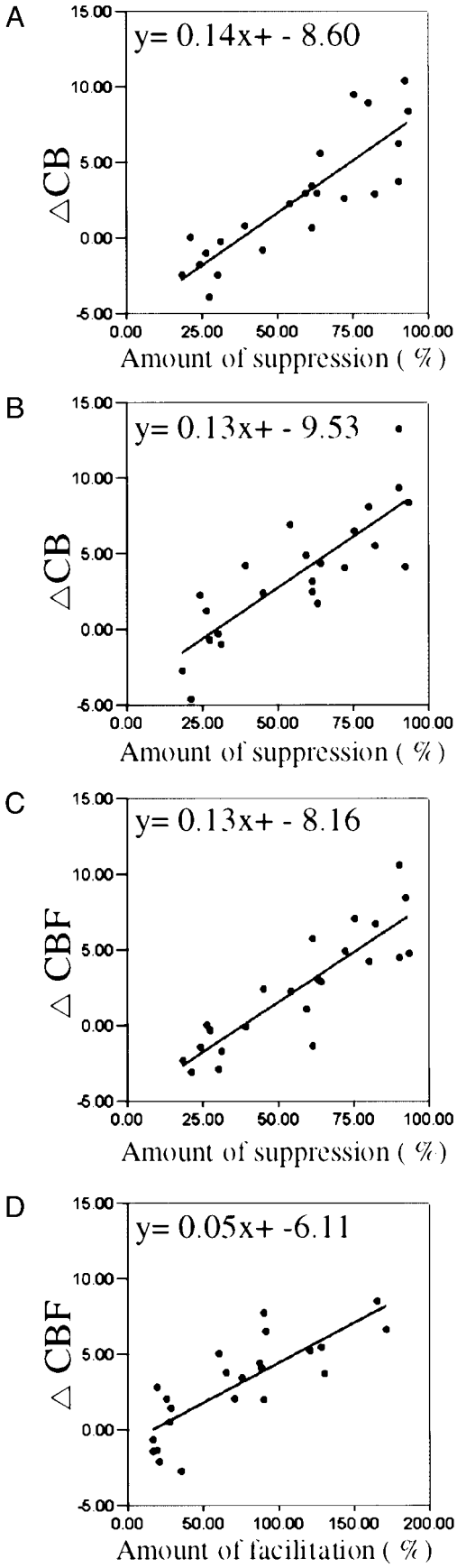
the scanner's patient port was used as a shield (Paus et al. 1997). A blank transmission scan was performed with the magnetic shielding in place before the subject was scanned. Once the subject and the coil assembly were positioned in the scanner, a 10-min transmission scan was performed. The transmission data were used to correct for the attenuation of gamma rays due to all objects in the scanner, including the coil, the coil mount, and metal sheets, and to determine the coil position relative to the subject's head.

Data analysis

CBF and peak-to-peak MEP amplitudes were measured over the 60-s scanning period. The size of the mean conditioned MEP response at 3-ms ISI (MEP3) and 12-ms ISI (MEP12) was expressed as a percentage of the size of the mean MEP response obtained by single pulse TMS (MEPsing). MEP values are expressed as means ± SD; statistical analysis was performed by means of repeated measures ANOVA and two-tailed Student's paired *t*-tests. To assess TMS-induced changes in CBF, a *t*-statistic map was generated by first subtracting the single-pulse TMS condition from the 3- and 12-ms paired-pulse TMS, respectively [TMS3 (A, B, C)—TMSsing (A, B, C); TMS12 (A, B, C)—TMSsing (A, B, C)]. The CBF differences were correlated with the relative amount of suppression [(1 − MEP3/MEPsing) × 100] and facilitation [(MEP12/MEPsing − 1) × 100] of the EMG responses. The calculations were carried out for each of the 3-D volume elements (voxels) constituting the entire volume. A *t*-statistic map was generated that tested whether at a given voxel the slope of the regression was significantly different from zero. The presence of a significant peak was evaluated by a method based on a 3-D Gaussian random-field theory, with correction for the multiple comparisons involved in searching the entire volume (Worsley et al. 1992). Values equal to or exceeding a criterion of $t = 3.5$ were considered significant ($P < 0.0004$, 2-tailed, uncorrected) for a brain volume of 1,500 ccm.

RESULTS

The mean intensity of the conditioning stimulus was 39.0 ± 2.4 (mean ± SE) of the maximum stimulator output delivered via the Bistim module. The mean intensity of the test stimulus



was 51.6 ± 2.2. Figure 1*A* demonstrates the effect of paired-pulse TMS in a single subject. Figure 1*B* shows the mean effect of paired-pulse stimulation on MEP response for all eight subjects [$F(1, 22) = 103$, $P < 0.001$]. With the subjects completely at rest in the scanner, the conditioning stimulus suppressed the test response at 3-ms ISI ($P < 0.01$) and facilitated it at 12-ms ISI ($P < 0.01$).

Table 1 summarizes the main findings obtained by correlating CBF differences with the amount of suppression and facilitation of EMG responses on a voxel-by-voxel basis. During 3-ms paired-pulse stimulation, significant positive correlations were observed between TMS3-TMSsing blood-flow differences and the amount of MEP suppression in the left M1, left lateral premotor cortex, and right M1 (Fig. 2). CBF values were extracted from a spherical volume of interest (VOI, radius 7 mm) centered at the *x*, *y*, and *z* coordinates of the statistical peaks defined by the regression map. Plotting these CBF values against the amount of suppression demonstrated that the CBF difference between TMS3-TMSsing conditions increased as function of the amount of EMG suppression (Fig. 3, *A–C*); the greater the amount of suppression, the larger the blood-flow difference. During 12-ms paired-pulse stimulation, a significant positive correlation was observed between TMS12-TMSsing blood-flow differences and the amount of MEP facilitation in the left M1 (Fig. 2). CBF values were extracted from a spherical VOI (radius 7 mm) centered at the *x*, *y*, and *z* coordinates of the statistical peak defined by the regression map. Plotting the CBF values against the amount of facilitation showed that CBF difference between the TMS12 and TMSsing conditions increased as function of the amount of EMG facilitation (Fig. 3*D*); the greater the facilitation, the larger the blood-flow difference. The slope of the regression line between the amount of the EMG suppression and CBF differences obtained in the TMS3-TMSsing condition were significantly greater ($P < 0.01$) than those between the amount of EMG facilitation and CBF differences obtained in the TMS12-TMSsing condition (Fig. 3, *A* and *B*).

DISCUSSION

The EMG analysis confirmed previous reports (Kujirai et al. 1993; Nakamura et al. 1997; Ziemann et al. 1996) in that a subthreshold conditioning stimulus applied over M1 produced a suppression and facilitation of MEP response elicited by a subsequent suprathreshold test stimulus given 3 and 12 ms later, respectively (Fig. 1, *A* and *B*). The PET results showed significant positive correlations of the CBF difference between the TMS3 and TMSsing conditions with the amount of suppression of EMG response (Fig. 3, *A–C*), and of CBF difference between the TMS12 and TMSsing conditions with the amount of facilitation of EMG response (Fig. 3*D*). These findings indicate that the stronger the inhibition/facilitation of EMG response, the higher the increase in local CBF.

FIG. 3. CBF values extracted using a spherical volume of interest (VOI, radius 7 mm) centered at the *x*, *y*, and *z* coordinates of the peaks defined by the regression map and plotted against the amount of suppression (*A–C*) and facilitation (*D*). With 3-ms paired-pulse TMS (*A–C*), CBF difference increased as function of the amount of EMG suppression; with 12-ms paired-pulse TMS (*D*), CBF difference increased as function of the amount of EMG facilitation. Notice the steeper trend of regression lines of the amount of EMG suppression in respect to CBF changes ($P < 0.01$). *A*: left M1. *B*: left lateral premotor cortex. *C*: right M1. *D*: left M1.

Anatomical studies of neuronal circuits of the neocortex have shown that both excitatory and inhibitory interneurons are modulated by cortico-cortical and thalamo-cortical connections through glutaminergic synapses (Eccles 1984). Inhibition and facilitation of the MEPs at 3 and 12-ms ISI are believed to be generated by cortical elements, such as cortico-cortical connections, oriented parallel to the surface of the brain (Amassian et al. 1987; Day et al. 1989; Nakamura et al. 1997; Rothwell 1997). It is likely that the activation of such fibers by our conditioning stimulus induced release of glutamate that activated both excitatory and inhibitory interneurons. Glutamate release is known to be associated with the production of nitric oxide (NO) and, in turn, with local increases in CBF (Faraci and Brian 1994).

Changes in CBF in left M1 obtained during 3- and 12-ms ISI conditions did not overlap, being about 13 mm apart in the dorsal-ventral direction (Fig. 2). This is consistent with previous neurophysiological studies with subdural electrodes in humans (Ashby et al. 1999) that showed that the sites of the conditioning stimuli producing inhibition and facilitation were not identical. It might also be possible that 3- and 12-ms paired-pulse TMS differentially affected distinct sites of the FDI representation. In the 3-ms paired-pulse TMS condition, we also observed CBF changes in regions distal from the stimulation side, namely in the left lateral premotor cortex and right M1 (Fig. 2); such changes were not detected in the 12- ms paired-pulse TMS condition. Since our study was performed with a large round coil, there is a possibility that CBF changes obtained with 3-ms paired-pulse TMS over the left lateral premotor cortex were related to direct stimulation of the cortex by the part of the coil located over this area (Fig. 2). However, if this were the case, then one would expect to see CBF changes in the 12-ms paired-pulse TMS condition also. Therefore such CBF changes may reflect changes in synaptic activity within an interconnected neural system. Since the early inhibition and late facilitation are thought to arise from separate pools of cortical interneurons (Ziemann et al. 1996), our findings might reflect different properties of the two separate pools. In support of this hypothesis, previous paired-pulse TMS studies showed that conditioning stimuli delivered at a site anterior (4–6 cm) to M1/S1 (where the test stimulus was applied) produced significant inhibition of the test MEP (Amassian et al. 1999; Civardi et al. 2000). These authors interpreted this finding as reflecting activation of cortico-cortical connections between the premotor/SMA region and sensorimotor cortex. The additional CBF changes in the contralateral M1 observed in our study in the 3-ms paired-pulse TMS condition may be related to the activation of transcallosal connections mediating interhemispheric inhibition (Di Lazzaro et al. 1999; Ferbert et al. 1992). The finding of a significant steeper slope of the regression line between CBF difference and amount of EMG suppression in the 3-ms TMS condition suggests that there is a higher probability of TMS-induced activation of inhibitory circuits as compared with excitatory circuits (Fig. 3, *A–D*). This might again be related to the different neurophysiological features of cortical inhibition and facilitation (Ziemann et al. 1996).

The MEPs obtained with 3- and 12-ms paired-pulse TMS are associated, respectively, with a smaller and larger muscle twitch and, presumably, a differential sensory feedback from the hand muscles to the contralateral sensorimotor cortex. This feedback could conceivably confound the blood-flow response to TMS observed at the stimulation site. But several features of our data argue against this possibility. First of all, both the amount of suppression and facilitation of TMS-elicited EMG responses were associated with an increase in blood-flow differences at the stimulation site. This means that, during 3-ms paired-pulse TMS, blood-flow differences were bigger in scans in which the muscle twitches were smaller. Second, no CBF changes were observed in the left sensory thalamus in any of the analyses, suggesting that the possible effects of muscle twitches on neural activity in sensory structures were undetectable in this study. Finally, the positive correlations between the amount of suppression and blood-flow differences in cortical regions other than contralateral sensorimotor cortex also argue against the simple effect of sensory afferents on the observed cortical response to paired-pulse TMS described here.

In conclusion, our study is the first to demonstrate CBF changes induced by paired-pulse TMS. The combined TMS/PET approach provides additional evidence for the role of intracortical mechanisms in TMS-induced suppression and facilitation of EMG response and allowed us to assess TMS-induced modulation of synaptic activity in cortical regions functionally connected with M1. The different modulation of CBF obtained with 3- and 12-ms ISIs, respectively, confirms that these two phenomena arise from separate pools of cortical interneurons.

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