

Dose-Dependent Reduction of Cerebral Blood Flow During Rapid-Rate Transcranial Magnetic Stimulation of the Human Sensorimotor Cortex

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Paus, Tomáš, Robert Jech, Christopher J. Thompson, Roch Comeau, Terry Peters, and Alan C. Evans. Dose-dependent reduction of cerebral blood flow during rapid-rate transcranial magnetic stimulation of the human sensorimotor cortex. *J. Neurophysiol.* 79: 1102–1107, 1998. Rapid-rate transcranial magnetic stimulation (rTMS) was used to stimulate the primary sensorimotor cortex in six healthy volunteers while regional changes in cerebral blood flow (CBF) were simultaneously measured by means of positron emission tomography. A figure-eight TMS coil (Cadwell Corticoil) was positioned, using frameless stereotaxy, over the probabilistic location of the left primary sensorimotor cortex, and a series of brief 10-Hz trains of TMS was delivered at subthreshold intensity during each of six 60-s scans. The scans differed in the number of trains delivered, namely 5, 10, 15, 20, 25, and 30 trains/scan, respectively. In the left primary sensorimotor cortex, CBF covaried significantly and negatively with the number of stimulus trains. These CBF decreases may reflect TMS-induced activation of local inhibitory mechanisms known to play a role in TMS-related phenomena, such as the electromyographic silent period.

INTRODUCTION

A focal single-pulse transcranial magnetic stimulation (TMS) of the human motor cortex typically increases electromyographic (EMG) activity in relaxed muscles (Barker et al. 1985; Cracco et al. 1993; Hallett and Cohen 1989). During voluntary contraction, however, the same TMS stimulus produces a prolonged postexcitatory inhibition of muscle activity, i.e. a silent period (Amassian et al. 1990; Triggs et al. 1992). Similarly, when a suprathreshold test pulse is preceded by a subthreshold one, the EMG response to the test stimulus is reduced (Kujirai et al. 1993; Wassermann et al. 1996a). It is believed that intracortical inhibitory mechanisms underlie, at least in part, such TMS-induced suppression of EMG activity. The involvement of the intracortical rather than spinal mechanisms has been inferred from studies comparing the effects of central and peripheral stimulation on EMG activity and spinal reflexes (Brasil-Neto et al. 1995; Sabatino et al. 1995) as well as from pharmacological (Ziemann et al. 1996) and lesion (Schnitzler and Benecke 1994; von Giesen et al. 1994) studies.

In this report we provide evidence for TMS-induced reduction in cerebral blood flow (CBF) and, by inference, synaptic activity in the human sensorimotor cortex. By using positron emission tomography (PET), changes in CBF were measured during brief trains of subthreshold rapid-rate TMS applied over the left primary sensorimotor cortex. We found significant decreases in CBF in the brain tissue under the

stimulating coil that varied as a function of the amount of stimulation.

METHODS

Experimental design

In six healthy volunteers, a figure-eight TMS coil was positioned over either the left primary sensorimotor cortex (M1/S1) or the left frontal eye-field (FEF); the FEF findings have been reported elsewhere (Paus et al. 1997). For each condition, CBF was measured in six 60-s ¹⁵O-H₂O scans acquired with the CTI/Siemens HR+tomograph. During the scan the subjects kept their eyes closed and white noise (80-dB SPL) was played through insert earphones to mask the coil-generated clicks. The subjects were instructed to relax and not to move during the scan. The EMG was recorded with surface electrodes placed over muscles of the right anterior forearm (flexor carpi radialis and palmaris longus), posterior forearm (extensor carpi radialis and brachioradialis), and the thenar (flexor pollicis brevis and abductor pollicis brevis). To allow for a correlational analysis of CBF data, a different number of TMS pulse-trains was delivered in the six scans, namely 5, 10, 15, 20, 25, and 30 pulse-trains per scan. The order of scans was randomized within each condition, and the order of conditions (M1/S1 and FEF) was counterbalanced across subjects.

Subjects

Four female and two male subjects volunteered for the study after giving written informed consent [average age 28 ± 6.5 (SD) yr]. All subjects, but one, were right-handed. Following the safety guidelines for the use of a rapid-rate TMS in normal volunteers (Pascual-Leone et al. 1993), the subjects were screened for a history of neurological disorders, in particular personal and family history of epilepsy. The study was approved by the Research and Ethics Committee of the Montreal Neurological Institute and Hospital.

Transcranial magnetic stimulation

The Cadwell high-speed magnetic stimulator and the Cadwell figure-eight coil (Corticoil, 2 tear-shaped coils of ~5-cm diam each) were used to produce a focal stimulation of the cerebral cortex through the skull. The duration of a single TMS pulse was 200 μs; the pulses were delivered in five pulse-trains of 400-ms duration each (between-pulse interval of 100 ms; i.e., a stimulation frequency of 10 Hz). A different number of pulse-trains was delivered in six 60-s scans, namely 5, 10, 15, 20, 25, and 30 pulse-trains. The shortest between-train interval was 1,600 ms. The intensity of stimulation was set at 70% of the maximum output of the stimulator. For the figure-eight coil used in this study, the estimated volume of stimulated tissue was 20 × 20 × 10 mm, with the point

of maximum stimulation being under the central junction of the two round coils (Cohen et al. 1990; Maccabee et al. 1990; Wassermann et al. 1996b).

Location of the target region and positioning of the TMS coil

To target the same area in all our subjects, we developed a procedure that took advantage of the standardized stereotaxic space of Talairach and Tournoux (1988) and frameless stereotaxy (Peters et al. 1996). 1) A three-dimensional magnetic resonance image (MRI) of the subject's brain is acquired and transformed into the standardized stereotaxic space with an automatic feature-detection algorithm (Collins et al. 1994); the MRIs (160 contiguous 1-mm-thick sagittal slices) were obtained from a Philips Gyroscan ACS-II (1.5 T). 2) An average, probabilistic location of the left M1/S1 in stereotaxic space is derived through a metanalysis of previous blood flow activation studies (see last paragraph of this section). 3) This location, defined by X, Y, and Z coordinates, is transformed to the subject's brain-coordinate "native" space, using an inverse version of the native-to-stereotaxic transformation matrix. This procedure allows us to determine where the target region is located in a given subject and, therefore, where to aim the coil during the experiment. The final step requires us to position the coil over this location, now marked on the MRI, with the aid of frameless stereotaxy. With the subject lying on the couch in the scanner, the subject's head is registered with the MRI and the coil is placed over the target location. Accurate positional and angular placement of the coil is achieved by interfacing it to the computer-linked probe of the frameless stereotaxy unit (Viewing Wand, ISG Technologies, Mississauga, Ontario, Canada). In this manner, the investigator can view the coil movement relative to the subject's MRI. When this location is reached, the coil is locked in place and the PET session begins.

The average location of the left M1/S1 in the standardized stereotaxic space (i.e., $X = -31$, $Y = -22$, and $Z = 52$) was derived from eight previous blood flow activation studies that involved finger movements of the right hand (Colebatch et al. 1991; Dettmers et al. 1995; Grafton et al. 1993; Jahanshahi et al. 1995; Jenkins et al. 1994; Matelli et al. 1993; Paus et al. 1993; Schlaug et al. 1994). The figure-eight coil was positioned over this location so that its anterior-posterior axis was parallel to the interhemispheric fissure, the handle of the coil was pointing in the anterior direction (i.e., towards the nose), and the plane of the coil was tangential to the skull.

Positron emission tomography

PET scans were obtained with a CTI/Siemens HR + 63-slice tomograph operated in a 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 were injected into the left antecubital vein. The CBF images were reconstructed with a 14-mm Hanning filter, normalized for differences in global CBF (henceforth "normalized CBF"), coregistered with the individual MRIs (Woods et al. 1993) and transformed into 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 insert consisting of four layers of 0.5-mm-thick mu-metal was formed in a cylinder whose outer diameter matched the inner diameter of the scanner's patient port (see Paus et al. 1997 for details). The sheets caused increased attenuation and resulted in a 22% loss in coincidence counts when inserted. 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 attenuation of gamma rays due to all objects in the scanner, including the coil, the coil mount, and the metal sheets.

To assess the significance of the relationship between the number of TMS pulse-trains and normalized CBF (i.e., their linear regression), the following calculations were carried out for each of the 3-D elements (voxels) constituting a volume. The dataset consisted of normalized CBF obtained in six subjects, scanned six times each during the TMS, yielding a total of 36 CBF volumes. The effect of TMS rate on CBF was assessed by means of an analysis of covariance (Sokal and Rohlf 1981), with subjects as a main effect and the number of pulse-trains administered during the scan as a covariate. The subject effect was removed and the parameter of interest was the slope of the effect of the number of pulse-trains on normalized CBF. 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, which corrects for the multiple comparisons involved in searching across a volume (Worsley et al. 1992). Values equal to or exceeding a criterion of $t = 4.0$ were considered as significant ($P < 0.0001$, 2-tailed, uncorrected), yielding a false positive rate of 0.37 in 555 resolution elements (each of which has dimensions $14 \times 14 \times 14$ mm) if the brain volume is $1,500.00 \text{ cm}^3$.

RESULTS AND DISCUSSION

The brief trains of TMS applied during the scanning elicited neither overt hand movement nor significant EMG response. The subjects did not report any sensations related to the stimulation, except for the tapping of the coil over their heads and hearing, to a varying degree, the clicks generated by the coil. The lack of TMS-induced changes in muscle activity is not surprising, given the relatively low intensity of stimulation and the constant position of the coil across all six subjects. One needs to fine-tune the orientation and angulation of the coil to activate corticospinal fibers and thus elicit EMG response with the lowest possible intensity (e.g., Cracco et al. 1993). In this study we preferred to minimize variations in the coil position, orientation, and angulation across the six subjects rather than to optimize these parameters in each individual to elicit EMG response. Nonetheless, our findings show that such subthreshold TMS of the left M1/S1 resulted in a significant modulation of CBF in this region; CBF decreased as a function of the number of pulse-trains delivered during a given scan (Figs. 1 and 2). In addition to the local under-the-coil changes in CBF, we also observed TMS effects on CBF in several regions distal from the stimulation site, including the supplementary motor area and the medial parietal region (Table 1). These effects most likely reflect changes in brain activity within an interconnected neural system. The use of the combined TMS/PET approach for studying neural connectivity was addressed in a previous paper (Paus et al. 1997). No significant positive covariations between the number of pulse-trains and CBF were observed in this study.

The TMS-related decreases in the M1/S1 blood flow may reflect modulation of the spontaneous excitatory synaptic activity in this region (e.g., Evarts 1981; Matsumura et al. 1988). There is considerable evidence to suggest that excitatory neurotransmission is associated with increased CBF, in part through mediation by local release of nitric oxide,

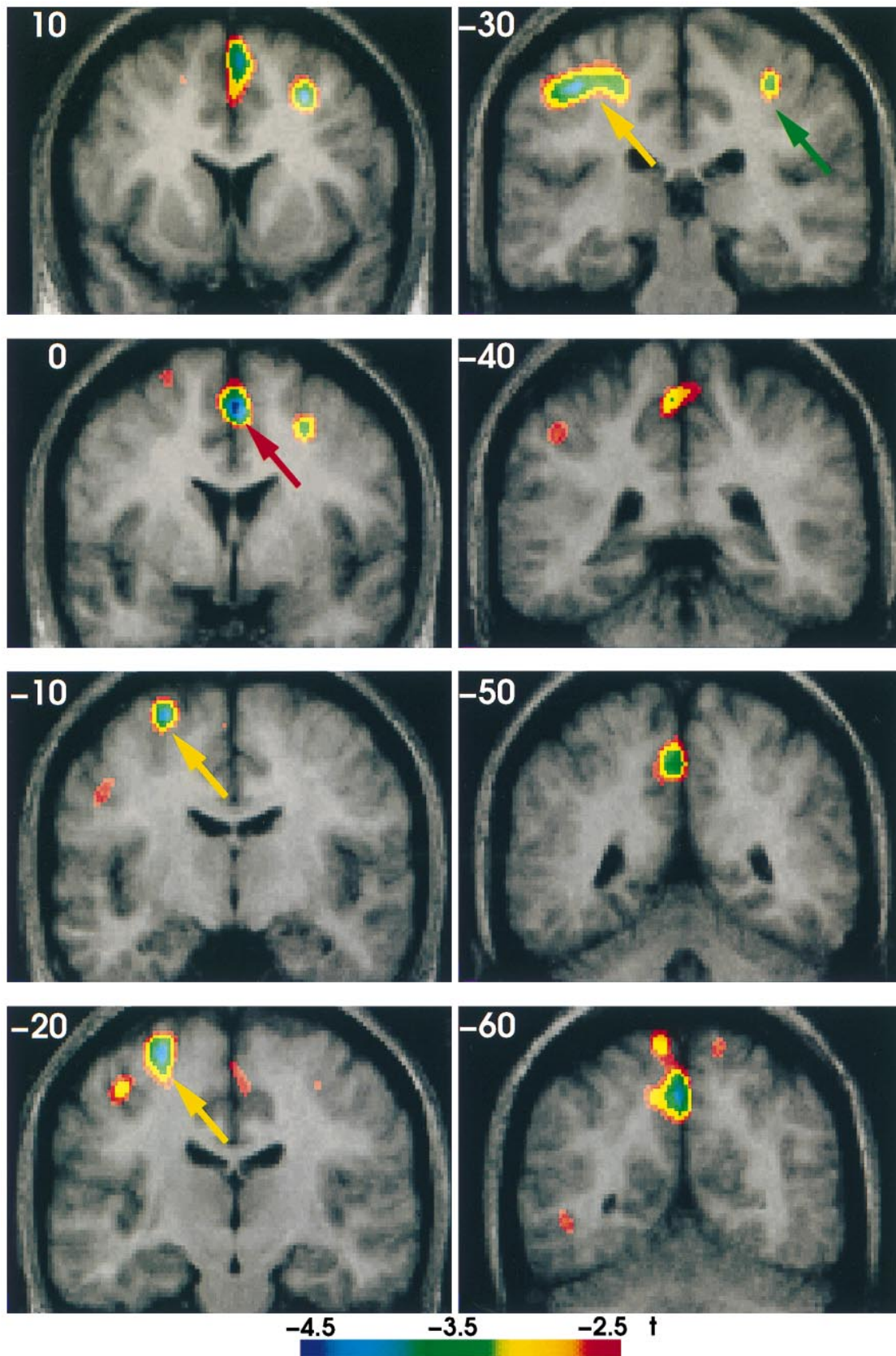


FIG. 1. Series of coronal sections through a merged position emission tomography/magnetic resonance imaging (PET/MRI) volume. The color-coded PET volume was thresholded ($t = -2.5$) showing the location of brain regions in which cerebral blood flow (CBF) covaried significantly and negatively with the number of transcranial magnetic stimulation (TMS) pulse-trains applied during the scan. The number in the *top left* corner of each section indicates its position (i.e., the Y coordinate, in mm) relative to the anterior commissure ($Y = 0$). Red arrow points to CBF covariations in the supplementary motor area, yellow arrows point to covariance peaks in and around the stimulation site (i.e., M1/S1), and green arrow points to CBF change in the M1/S1 contralateral to the stimulation site.

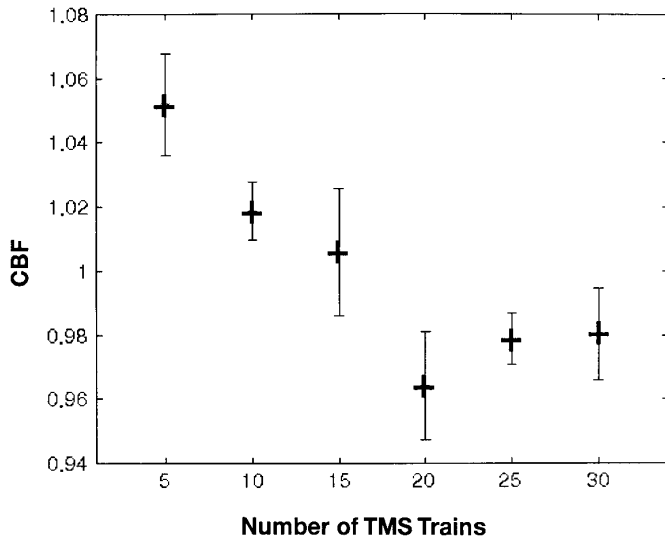


FIG 2. Mean \pm SE CBF values extracted from a spherical volume-of-interest centered at one of the regression peaks (left central sulcus, $X = -24$, $Y = -27$, and $Z = 50$) yielded at the stimulation site, plotted against the number of TMS pulse-trains.

and that increases or decreases in excitatory transmission would be reflected in increases or decreases in CBF (Knowles et al. 1989; Northington et al. 1992; Roland 1993). Decreases in CBF have also been shown as a result of pharmacological stimulation of γ -aminobutyric acid-A ($GABA_A$) receptors, suggesting that inhibitory postsynaptic neurotransmission may be associated with decreases in CBF (Roland and Friberg 1988).

In previous studies performed with single-photon emission tomography or functional magnetic-resonance imaging, transcranial magnetic (Dressler et al. 1990; Shaffran et al. 1989) or electrical (Brandt et al. 1996) stimulation of M1 was shown to increase brain perfusion in the cortex under the coil or electrode, respectively. These studies differed from the current study in that they all used suprathreshold stimuli administered as single pulses with a minimum between-pulse interval of 1 s. It is likely that the short (100 ms) between-pulse interval used in our study, as well as the burst nature of the stimulation (5 pulses administered within 400 ms) and its low intensity, contributed to the observed local decreases in CBF. The fact that we used a low (sub-threshold) intensity of stimulation may be critical in view of the reported increases in the amplitude of motor-evoked potentials during suprathreshold high-frequency (5, 10, and 20 Hz) TMS of the motor cortex (Pascual-Leone et al.

1994). On the other hand, it has been shown that subthreshold "conditioning" stimulation of the motor cortex is highly effective in suppressing EMG response to the subsequent suprathreshold stimulation (Kujirai et al. 1993). Thus a particular combination of TMS parameters, including the intensity, frequency, and duration of stimulation, may be critical for a preferential activation of distinct neuronal pools in the stimulated volume. In the case of the motor cortex, the inhibitory neurotransmitter GABA is utilized by the majority of nonpyramidal neurons, thus providing a powerful mechanism for the spatiotemporal coordination of muscle activity (Asanuma and Rosen 1973; DeFelipe and Jones 1985; Matsumura et al. 1991; Stefanis and Jasper 1964; for review see Keller 1993). It is possible that in this study trains of 10-Hz subthreshold TMS resulted in a prevailing activation of local inhibitory mechanisms and a subsequent reduction of excitatory synaptic activity in and around the stimulated region. This interpretation is consistent with the possibility that local decreases in CBF reflect decreases in excitatory synaptic activity (see above). It should be pointed out that an identical stimulation of the left FEF resulted in CBF increases both under the coil and in the related circuitry (Paus et al. 1997). The stimulation sites for these separate experiments are located in close proximity, with the FEF being about 20-mm anterior to M1/S1. We would therefore suggest that the type of CBF response to the rapid-rate TMS probably depends on the type of local neural circuitry within the stimulated region.

In conclusion, our findings provide additional evidence for the role of intracortical mechanisms in TMS-induced suppression of muscle activity. In general, the important advantage of the combined TMS/PET approach is that it now allows one to assess TMS-induced modulation of synaptic activity in cortical regions other than M1. As such it may prove useful for quantifying changes in cortical excitability in relation to various experimental or clinical interventions or associated with certain diseases of the brain.

We thank the Cadwell laboratories for providing us with the high-speed magnetic stimulator and the technical advice of engineer M. Vance. We also thank B. Hynes and M. Mazza from the Montreal Neurological Institute (MNI)/Hospital for building the coil-probe assembly, R. Visca for assistance with various aspects of the project, and the staff of the McConnell Brain Imaging Center for highly professional assistance in data acquisition and preprocessing. We also thank Drs. Brenda Milner and Gabriel Leonard for comments on the manuscript.

This work was supported by the McDonnell-Pew Program in Cognitive Neuroscience and Medical Research Council (Canada) special project SP-30. Dr. Jech's stay at the MNI was funded by the Granting Agency of the

TABLE 1. Brain regions with significant negative covariations between normalized CBF and the number of TMS pulse-trains

Region	BA	X	Y	Z	t
Left central sulcus*	4	-24	-27	50	-4.2
Left precentral gyrus*	4	-26	-16	63	-4.4
Left postcentral gyrus*	2	-41	-29	48	-4.1
Right superior frontal sulcus (premotor)	6	28	5	47	-4.7
Medial frontal gyrus (SMA)	6	2	3	56	-4.9
Medial parietal lobule	7	-3	-56	45	-4.5
Right central sulcus	4/2	34	-31	50	-3.7

TMS target location at $X = -31$, $Y = -22$, and $Z = 52$. CBF, cerebral blood flow; TMS, transcranial magnetic stimulation; BA, Brodmann's cytoarchitectonic areas approximated according to the Talairach and Tournoux atlas (Talairach and Tournoux 1988); SMA, supplementary motor area. * Marks peaks located near the TMS target.

Czech Republic (GACR 0376) and the Czech Ministry of Health (IGA MZ 35-71-31 and IGA MZ 35-72-3).

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Received 14 July 1997; accepted in final form 29 October 1997.

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