Synchronization of Neuronal Activity in the Human Primary Motor Cortex by Transcranial Magnetic Stimulation: An EEG Study

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Paus, T., P. K. Sipila, and A. P. Strafella. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. *J Neurophysiol* 86: 1983–1990, 2001. Using multichannel electroencephalography (EEG), we investigated temporal dynamics of the cortical response to transcranial magnetic stimulation (TMS). TMS was applied over the left primary motor cortex (M1) of healthy volunteers, intermixing single suprathreshold pulses with pairs of sub- and suprathreshold pulses and simultaneously recording EEG from 60 scalp electrodes. Averaging of EEG data time locked to the onset of TMS pulses yielded a waveform consisting of a positive peak (30 ms after the pulse P30), followed by two negative peaks [at 45 (N45) and 100 ms]. Peak-to-peak amplitude of the P30–N45 waveform was high, ranging from 12 to 70 μV; in most subjects, the N45 potential could be identified in single EEG traces. Spectral analysis revealed that single-pulse TMS induced a brief period of synchronized activity in the beta range (15–30 Hz) in the vicinity of the stimulation site; again, this oscillatory response was apparent not only in the EEG averages but also in single traces. Both the N45 and the oscillatory response were lower in amplitude in the 12-ms (but not 3-ms) paired-pulse trials, compared with the single-pulse trials. These findings are consistent with the possibility that TMS applied to M1 induces transient synchronization of spontaneous activity of cortical neurons within the 15- to 30-Hz frequency range. As such, they corroborate previous studies of cortical oscillations in the motor cortex and point to the potential of the combined TMS/EEG approach for further investigations of cortical rhythms in the human brain.

INTRODUCTION

Synchronization of neuronal activity within and across different cortical regions may provide a means for the binding of information processed in specialized cortical modules. In the visual system, high-frequency (40–60 Hz) oscillations in neural activity are believed to facilitate information processing that underlies perceptual analysis of complex visual scenes, as well as that underlying perceptual learning (Singer 1993). Similar oscillations occur in the primate sensorimotor cortex, with the dominant frequency range being 15–30 Hz ("beta" rhythm). The predominance of the beta rhythm over the precentral region was first reported by Jasper and Andrews (1938) with scalp electroencephalography (EEG); Jasper and Penfield subsequently confirmed these findings with electrocorticography (Jasper and Penfield 1949). More recently, spontaneous oscillations in this frequency range occurring at rest have been studied with EEG (Pfurtscheller 1992) and magnetoencephalography (MEG) (Hari and Salmelin 1997; Salmelin and Hari 1994a,b). Furthermore, coherence between EEG/MEG signal and electromyogram (EMG) has been described as occurring particularly in the 15- to 30-Hz frequency band (Brown et al. 1998; Conway et al. 1995; Hari and Salenius 1999; Mima et al. 2000; Salenius et al. 1997). Marsden et al. (2000) confirmed these observations in patients by recording electrical activity directly from the cortex.

The oscillations described above could be generated by local cortical neurons, perhaps due to their intrinsic membrane properties or to local intracortical connections (see, for example, Gray et al. 1992). Stimulating the sensorimotor cortex while recording its activity may further advance this hypothesis; such stimulation could be expected to trigger an oscillation and/or to reset the ongoing rhythmic activity of a local pacemaker. In this study, we applied transcranial magnetic stimulation (TMS) over the primary sensorimotor cortex in healthy volunteers and observed an EEG response that was consistent with TMS-induced synchronization of EEG activity in the 15- to 30-Hz frequency range.

METHODS

Design

Single- and paired-pulse TMS of the left primary motor cortex (M1) was carried out during multichannel EEG recording in healthy volunteers. Each subject underwent a 1-h session consisting of six 5-min blocks, each containing 60 TMS trials. Single-pulse trials (n = 120) were intermixed with 3-ms (n = 120) and 12-ms (n = 120) trials of paired-pulse TMS; the intertrial interval was 4–6 s. To mask coil-generated clicks, white noise (90 dB) was played through insert earphones during the EEG recording. Subjects were seated in a comfortable armchair with their elbows flexed at 90°, hands pronated in a relaxed position, and eyes open. The subjects' heads were restrained in a chin and forehead rest. At the end of the TMS session, peripheral stimulation of the ulnar nerve was applied to compare evoked potentials related to somatosensory stimulation with those elicited by TMS.

Subjects

Seven healthy volunteers (4 male; 20–38 yr; 1 left-handed) participated in the study. The study was approved by the Research Ethics

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Committee of the Montreal Neurological Institute and Hospital, and written informed consent was obtained from all participants.

TMS

TMS was carried out with two Magstim 200 magnetic stimulators connected by a Bistim module (Magstim, Whitland, Dyfed, UK). This device allows delivery of two magnetic pulses through the same coil with very short between-pulse intervals. 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 diameter) oriented so that the induced electric current flowed in a posterior-anterior direction over the left M1. The coil was held in a fixed position by a mechanical arm over the area where the lowest motor threshold was obtained. Motor-evoked potentials (MEPs) were recorded from the right first dorsal interosseous (FDI) muscle with Ag/AgCl surface electrodes fixed on the skin with a belly-tendon montage.

Motor threshold (MT) was determined for both relaxed (rMT) and tonically active (aMT) muscle. 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. While aMT was determined, subjects were instructed to maintain a steady muscle contraction of about 30% of their maximum voluntary contraction. Active MT was defined as the lowest stimulus intensity sufficient to elicit five MEPs of at least 50 μV averaged over 10 consecutive trials delivered at intervals longer than 5 s.

The intensity of single-pulse TMS was set to evoke an MEP of about 0.5 mV peak-to-peak amplitude in relaxed muscle. In the paired-pulse TMS trials, the intensity of the conditioning (subthreshold) stimulus was set 5% below aMT, and the intensity of the test (suprathreshold) stimulus was the same as that used in the single-pulse TMS trials. Two between-pulse intervals were used in the paired-pulse trials: 3 and 12 ms (Kujirai et al. 1993).

Peripheral electrical stimulation

Peripheral stimulation was carried out to investigate the similarity between centrally and peripherally induced muscle activation and the related somatosensory afference. Using a Grass constant-current stimulator, 100 electrical stimuli were applied with a bipolar electrode placed over the right ulnar nerve; the interstimulus interval was 3 s. The intensity of stimulation was adjusted so as to elicit MEPs of about 0.5–1.0 mV (constant current: 7.0–8.5 mA) in the right FDI.

EEG

EEG was recorded with a 60-channel TMS-compatible system (Virtanen et al. 1999), with the linked-mastoid used as the reference electrode. Saturation of the EEG amplifiers by the TMS pulse was prevented by using a sample-and-hold circuit that pins the amplifier output to a constant level for 2.5 ms, starting 100 μs before the pulse; the signal recovers ~3 ms after the pulse. Overheating of electrodes located in the vicinity of the stimulating coil (Roth et al. 1992) was minimized by using TMS-compatible Ag/AgCl-coated electrodes (8-mm diam, 0.5-mm thickness) with 2-mm slits to interrupt eddy currents. The ground electrode was placed on the forehead. Electrode impedance was measured with the Grass F-EZM4B-1 impedance meter and ensured to be below 5 kΩ. In several subjects, the locations of the electrodes were digitized with an optical tracking system (*BrainSight* by Rogue Research) and superimposed on a three-dimensional MRI dataset of the subject's head. The amplifiers' bandwidth was 0.1–500 Hz, and the signal was sampled at 1.45 kHz.

After rejection of EEG epochs containing large artifacts, the signal was averaged, and four times bicubic-interpolated potential maps were generated using MATLAB 5.2. CURRY 4.0 was used to model dipoles. The first 25 ms following the TMS pulse often contained large artifact, and these were removed from the EEG trace by zero padding.

In addition to the analysis of TMS-elicited evoked potentials, we used the temporal spectral evolution (TSE) technique (Salmelin and Hari 1994a) to characterize TMS-induced EEG rhythms. TSE waveforms were computed for each 2.8-s epoch (1.4 s before and 1.4 s after the TMS pulse) by band-pass filtering [Butterworth zero-phase 4th-order forward and reverse digital filtering (2nd-order forward and backward)] in the following 2-Hz frequency-bands: 15–17, 17–19, 19–21, 21–23, 23–25, 25–27, 27–29, and 29–31 Hz (see Pfurtscheller and Klimesch 1992 for similar use of 1- and 2-Hz frequency bands). The filtered epochs were full-wave rectified and averaged across trials.

EMG

EMG activity in the right FDI was recorded on the single EMG channel of the EEG system. The amplifiers' bandwidth was 0.1–500 Hz, and the signal was sampled at 1.45 kHz.

RESULTS

Spatial distribution and amplitude of TMS-elicited evoked potentials

The waveform elicited by single-pulse TMS consisted of a positive peak (30 ms P30), followed by two negative peaks [45 (N45) and 100 (N100) ms; Fig. 1, *A* and *B*]. The potential maps (Fig. 2*A*) revealed that the P30 component was distributed centrally, the N45 component formed a dipole centered over the stimulation site, and the N100 component had a wide distribution with slight predominance over the left central region. The location of the N45 dipole was confirmed with dipole modeling; the resulting dipole was oriented perpendicular to the central sulcus, with the positive pole lying posterior to the negative one (Fig. 2*B*).

The amplitudes of the evoked potentials (Table 1) were measured at the locations of their maxima; these were the vertex for both P30 and N45 and TP3 for N100. The intensity of single-pulse TMS correlated significantly with the absolute amplitude of N45 ($r = 0.67$, $P = 0.07$) but not with that of P30 [$r = 0.30$, not significant (n.s.)] or that of N100 ($r = 0.29$, n.s.). A significant correlation was also observed between the absolute amplitude of N45 and the intensity of the conditioning TMS stimulus ($r = 0.83$, $P = 0.01$). The amplitude of MEPs correlated significantly with the absolute amplitude of N100 ($r = 0.52$, $P < 0.05$) when calculated across the three conditions in the five subjects with reliable MEP data (see *Paired-pulse TMS:* EMG); the MEP-N100 correlations were similar in each of the three conditions when calculated separately (single pulse: $r = 0.58$; 3-ms paired-pulse: $r = 0.75$; 12-ms paired-pulse: $r = 0.68$; none of the correlations were significant). There was a significant relationship between the absolute amplitudes of P30 and N100 ($r = 0.78$, $P = 0.02$) but not between those of P30 and N45 ($r = 0.05$, n.s.) or those of N45 and N100 ($r = 0.36$, n.s.).

Latency of TMS-elicited evoked potentials

The latencies of the three components are also presented in Table 1. In five subjects, the amplitude of the N45 was large enough to allow detection of this potential in a high proportion of individual trials, i.e., without averaging (see Fig. 1*C* for an example from *subject PS*). The latency of N45 was measured

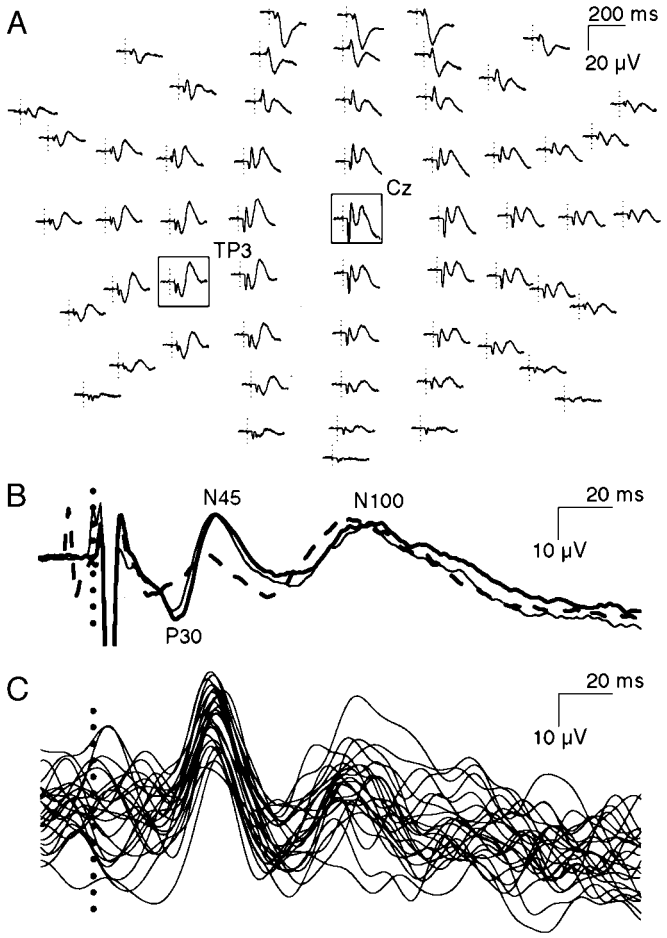

FIG. 1. *A*: grand average (7 subjects, 100–120 trials/subject) of the electroencephalography (EEG) response to single-pulse transcranial magnetic stimulation (TMS) at all scalp locations. *B*: grand average of the EEG response recorded at vertex in single-pulse (thick solid line), 3-ms paired-pulse (thin solid line) and 12-ms paired-pulse (dashed line) trials. *C*: 20 single traces of EEG randomly selected from 120 traces recorded during single-pulse TMS in 1 subject (*PS*). The dotted line indicates TMS onset.

in all these trials, and the mean ± SD was calculated for each of the five subjects with the following results (in ms): *AB*, 48.2 ± 3.4; *AG*, 46.9 ± 2.3; *KW*, 47.3 ± 3.4; *MI*, 48.4 ± 2.7; *PS*, 44.0 ± 1.6.

Temporal spectral evolution

Figure 3*B* illustrates TMS-induced oscillations in the 21- to 23-Hz and 23- to 25-Hz bands in one of the subjects (*AB*); the oscillations were obtained by averaging filtered and rectified EEG signal recorded in 120 single-pulse trials. The oscillation begins immediately after the pulse and is restricted to the vicinity of the stimulation (Fig. 3*B*, *bottom*). Table 1*D* indicates that such TMS-induced oscillations were observed in at least one of the 2-Hz bands for each of five subjects. The oscillatory response was virtually absent in the subjects with the lowest stimulation intensity and the lowest P30-N45 amplitude (*AS* and *TP*). The robustness of the oscillatory response time locked to the TMS pulse is apparent from its presence in individual EEG traces, which were filtered in the beta range (15–30 Hz) to compensate for the interindividual differences in the exact frequency of the oscillatory response (Fig. 4).

Paired-pulse TMS

EMG. In two subjects (*TP* and *PS*), the amplitude of MEPs elicited by single-pulse TMS in the right FDI fluctuated throughout the session, resulting in a high proportion (>50%) of trials with no EMG response in this muscle. These two subjects were therefore excluded from further analysis. In the remaining five subjects, the median of the MEP amplitude across 120 trials was calculated for each of the 3 conditions. The group means of these median values were 484 ± 68 μV (mean ± SD; single pulse), 226 ± 73 μV (3-ms paired pulse), and 556 ± 97 μV (12-ms paired pulse). Repeated-measures ANOVA confirmed that there was a significant effect of condition ($F_{2,15} = 6.3$, $P = 0.02$); pair-wise comparisons revealed significant differences between single-pulse and 3-ms paired-

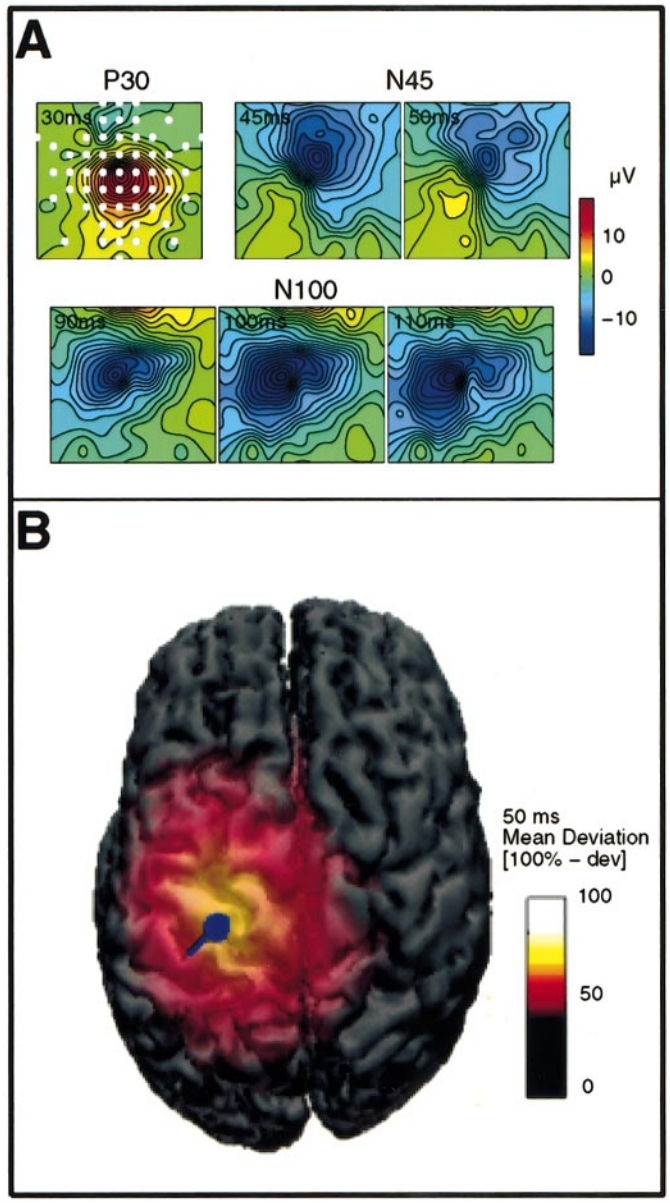

FIG. 2. *A*: scalp distribution of the grand-average potentials recorded during single-pulse TMS. Numbers in the *top left corner* of each map indicate time after the TMS pulse. *B*: CURRY-generated probability distribution of a dipole of the N45 negative potential and the best possible fit; note that the dipole is oriented perpendicular to the central sulcus, with the positive pole lying posterior to the negative one.

TABLE 1. *Amplitude and latency of scalp potentials and the amplitude of motor-evoked potentials*

Subject	TMS Intensity Test	MEP	P30 L	P30 A	N45 L	N45 A	N100 L	N100 A
			A. Single pulse					
AB	55	483	32.4	12.2	46.2	−12.4	111.3	−26.2
AG	60	273	34.7	7.3	45	−14.9	110.1	−12.5
AS	45	406	31.8	14.6	42.2	1.8	111.9	−9.1
KW	56	632	30.1	20.1	45.6	−14.7	98.6	−14.7
MI	62	626	28.3	70.5	45.6	0.5	117	−36.3
PS	66		30.1	11.4	43.3	−33.3	91.7	−12.6
TP	52		31.8	8.9	46.2	−3.5	94.6	−19.6
Mean	56.57 ± 6.92	484 ± 68	31.31 ± 2.05	20.71 ± 22.34	44.87 ± 1.54	−10.93 ± 12.11	105.03 ± 9.86	−18.71 ± 9.58

Subject	TMS Intensity Test	TMS Intensity Conditioning	MEP	P30 L	P30 A	N45 L	N45 A	N100 L	N100 A
				B. 3-ms paired-pulse					
AB	55	46	254	31.2	17.1	43.9	−9.6	113	−26.9
AG	60	46	331	32.9	8.2	43.3	−16.4	107.8	−13.6
AS	45	33	15	29.5	13.1	41.6	0.7	112.4	−7.7
KW	56	39	110	28.9	19.6	45	−16.8	96.9	−12.4
MI	62	42	418	27.1	59.9	45	−2.7	106.7	−26.9
PS	66	52		27.8	7.3	40.4	−31.1	91.7	−7.5
TP	52	37		31.2	4	43.9	−7.3	95.7	−24.8
Mean	56.57 ± 6.92	42.14 ± 6.41	226 ± 73	29.80 ± 2.07	18.46 ± 19.10	43.30 ± 1.72	−11.89 ± 10.67	103.46 ± 8.58	−17.11 ± 8.82

Subject	TMS Intensity Test	TMS Intensity Conditioning	MEP	P30 L	P30 A	N45 L	N45 A	N100 L	N100 A
				C. 12-ms paired-pulse					
AB	55	46	699	18	6.1	37	−1.2	102.1	−21.1
AG	60	46	733	18.5	9.6	34.7	−1.9	98	−15.2
AS	45	33	320	22	12.9	52	−0.9	110.7	−12.2
KW	56	39	319	21.4	7.7	39.3	−9.1	90.6	−11.9
MI	62	42	709	30.1	59.5	52.5	8.7	109	−31.8
PS	66	52		22	8.2	32.4	−16.1	96.9	−11.2
TP	52	37		33.5	−0.7	43.9	−10.5	93.4	−23.9
Mean	56.57 ± 6.92	42.14 ± 6.41	556 ± 97	23.64 ± 5.88	14.76 ± 20.16	41.69 ± 8.07	−4.43 ± 8.13	100.10 ± 7.59	−18.19 ± 7.74

Subject	TMS Intensity Test	P30/N45 Amplitude	Frequency Band, Hz 15–17	17–19	19–21	21–23	23–25	25–27	27–29	29–31
			D. Oscillatory response: single pulse							
AB	55	24	−	−	−	+	+	−	−	−
AG	60	22	+	+	−	−	−	−	−	−
AS	45	16	−	−	−	−	−	−	−	−
KW	56	35	+	−	−	−	−	−	−	−
MI	62	70	−	+	+	+	+	+	+	+
PS	66	44	+	+	+	+	+	+	−	−
TP	52	12	−	−	−	−	−	−	−	−

Subject	TMS Intensity Test	TMS Condition SP	3-ms	12-ms
	E. Amplitude of the oscillatory response			
AB	55	2.8	2.5	2.6
AG	60	2.9	3.4	3.0
AS	45			
KW	56	3.3	3.6	2.7
MI	62	4.9	4.6	4.3
PS	66	3.2	3.7	2.5
TP	52			

Values are means ± SD. P30, N45, N100, positive and negative scalp potentials peaking at 30, 45, and 100 ms after the suprathreshold transcranial magnetic stimulation (TMS) pulse, respectively; L, latency; A, amplitude; Test, intensity of the suprathreshold (test) stimulus; Conditioning, intensity of the subthreshold (conditioning) stimulus; P30/N45, peak-to-peak amplitude between the positive (P30) and negative (N45) peaks; SP, single pulse; 3-ms, paired-pulse TMS with 3-ms between-pulse interval; 12-ms, paired-pulse TMS with 12-ms between-pulse interval.

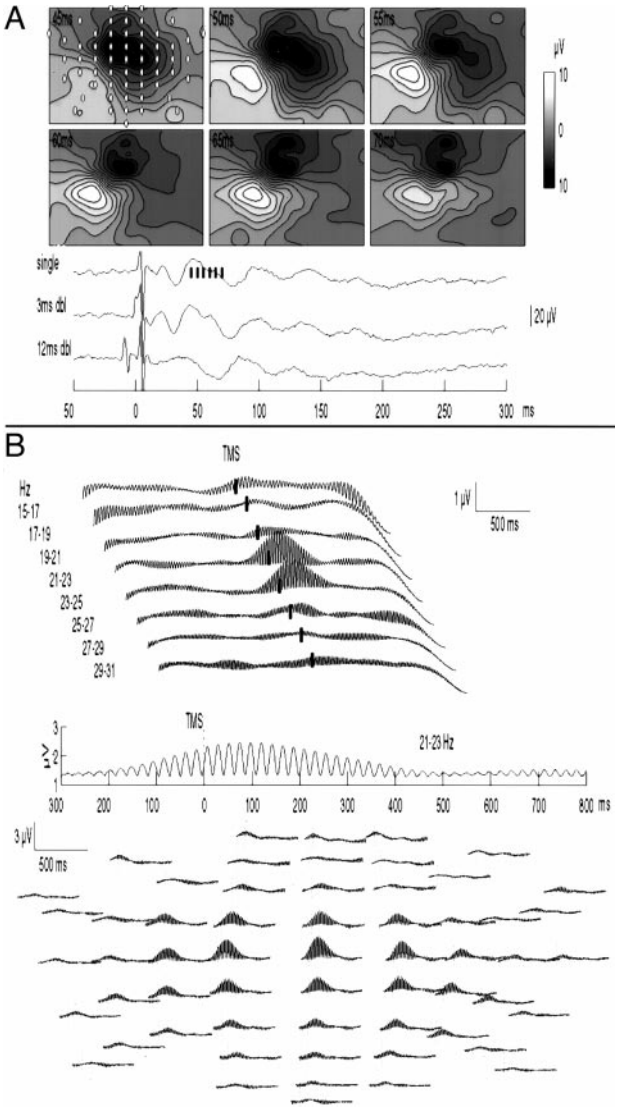

FIG. 3. *A*: scalp distribution (*top*) and waveforms (*bottom*) of average potentials recorded during single-pulse TMS (*top*) and single- as well as paired-pulse TMS (*bottom*) in one subject (*AB*). Note the reduction of the P30-N45 potential during 12-ms paired-pulse TMS. Also, note the periodicity (about 20 Hz) in the average waveform recorded during single-pulse and 3-ms paired-pulse TMS, and its attenuation during the 12-ms paired-pulse TMS. *B*: temporal evolution of filtered, rectified, and averaged EEG activity in the beta range (15–30 Hz), computed for each of eight 2-Hz bands, in 1 subject (*AB*) and the spatial distribution of the 21- to 25-Hz band (*bottom*). A vertical bar indicates the onset of the TMS pulse. Note that the onset of the oscillation appears to precede the TMS pulse; but this time difference is a technical one, resulting from the filtering. We used a simulated oscillation of similar amplitude and found that the filtered data preceded the onset of the simulated oscillation by the same amount of time. We conclude therefore that the oscillation begins immediately after the pulse.

pulse conditions ($P = 0.03$, 1-tailed), and between 3- and 12-ms paired-pulse conditions ($P < 0.001$, 1-tailed). The difference between the single-pulse and 12-ms paired-pulse conditions was not significant.

EEG. Table 1, *A–C*, and Fig. 1*B* contain EEG data obtained in the three TMS conditions, i.e., in single-pulse and 3- and 12-ms paired-pulse trials. No significant differences were observed between the single-pulse and 3-ms paired-pulse trials. On the other hand, absolute amplitudes of P30 ($t = 2.9$, $P = 0.01$) and N45 ($t = 1.99$, $P = 0.05$) were significantly reduced in the 12-ms paired-pulse trials, relative to the single-pulse TMS. The absolute amplitude of N100 was not significantly different in the single-pulse TMS and 12-ms paired-pulse conditions ($t = 0.36$, $P = 0.36$).

Table 1*E* contains data on the oscillatory response elicited by the test stimulus in single-pulse and 3- and 12-ms paired-pulse trials. Using a nonparametric statistical analysis in a subgroup of five subjects with a clear oscillatory response present in all three conditions, we found that the maximum amplitude of the oscillatory response was reduced in the 12-ms paired-pulse trials, compared with either the single-pulse ($z = 1.8$, $P = 0.04$, 1-tailed) or the 3-ms paired-pulse ($z = 1.8$, $P = 0.04$, 1-tailed) trials.

Evoked potentials to peripheral electrical stimulation

In six subjects, we were able to acquire EEG data during electrical stimulation of the right ulnar nerve (63–99 trials/subject). As can be seen in Fig. 5*C*, two negative components were observed, one at 65 ms (−5.7 μV) and another at 129 ms (−9.8 μV). The first component was more pronounced over the left parietotemporal region, i.e., contralateral to the stimulated nerve, while the second component had more widespread distribution with a maximum over the vertex.

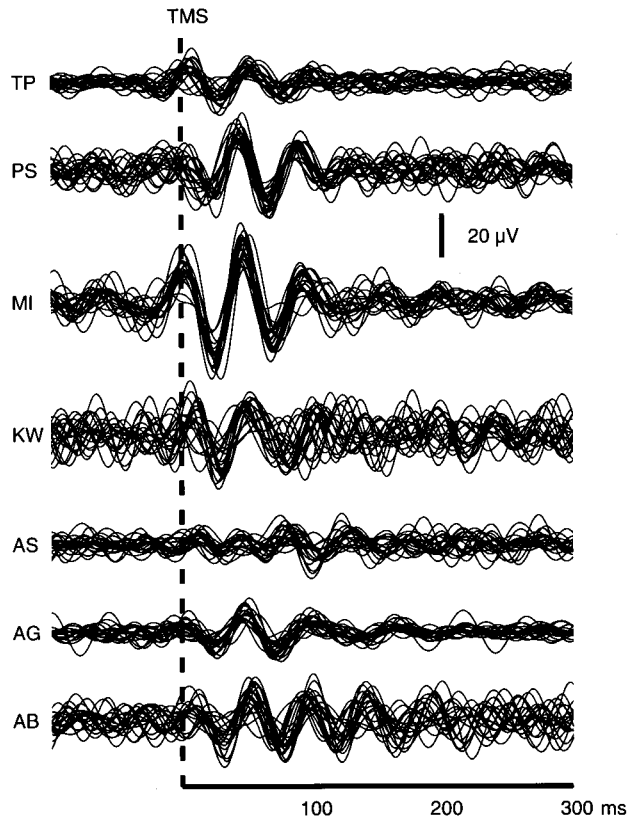

FIG. 4. Temporal evolution of EEG activity filtered in the beta range (15–30 Hz) using single traces recorded during single-pulse TMS in the 7 subjects; 20 traces are superimposed in each subject. Note that the onset of the oscillation appears to precede the TMS pulse; but this time difference is a technical one, resulting from the filtering (see Fig. 3 for details).

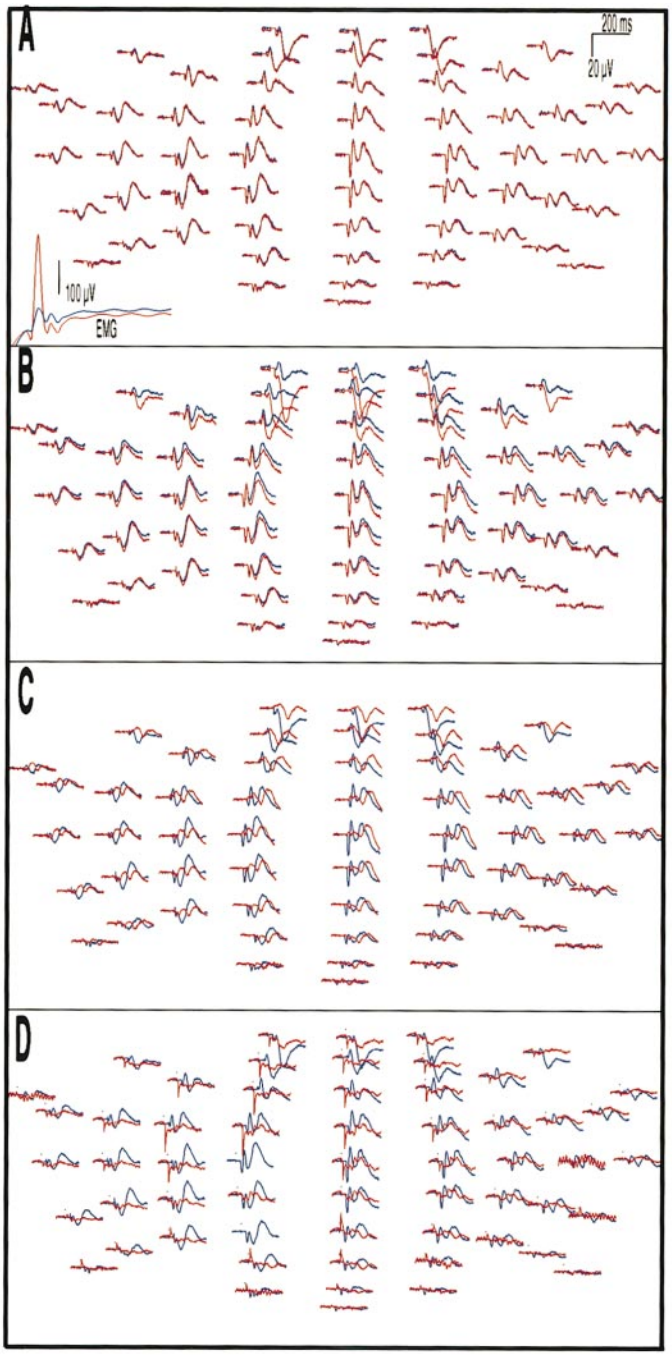

FIG. 5. Waveforms of grand-average potentials recorded during single-pulse TMS (*A* and *B*) and peripheral nerve stimulation (*C*). *A*: effect of TMS-elicited muscle twitch; trials were divided into those below (blue) and those above (red) the median value of the electromyogram (EMG) response elicited by suprathreshold TMS of the left M1. *B*: effect of eye movements; trials were divided into those below (blue) and those above (red) the median value of eye-movement–related positive deflection recorded between 60 and 120 ms in the middle most-anterior channel. *C*: effect of electrical stimulation of the right ulnar nerve; red trace corresponds to the somatosensory evoked potential (SEP) recorded during the ulnar stimulation. The SEP is plotted together with the grand-average potential recorded during single-pulse TMS (blue trace) to facilitate comparison of the two waveforms. *D*: effect of electrical stimulation of the scalp carried out in one subject; red trace corresponds to the SEP recorded during the scalp stimulation. The SEP is plotted together with the grand-average potential recorded during single-pulse TMS (blue trace) to facilitate comparison of the two waveforms.

Effect of TMS-induced EMG response on TMS-elicited evoked potentials

To investigate further the possibility that the TMS-elicited evoked potentials could be contaminated by the afferent input from the activated muscle, we divided all trials into those below and those above the median value of the EMG response. As can be seen on Fig. 5*A*, there was no difference between the evoked potentials recorded in trials with and without concomitant EMG response.

Effect of eye-movement artifacts on TMS-elicited evoked potentials

Eye-movement artifacts were present in a high proportion of trials, making it impractical to exclude such trials from the analysis. To investigate the effect of such artifacts on the TMS-elicited evoked potentials, we used the amplitude of the positive deflection occurring between 60 and 120 ms in the middle most-anterior channel as an index of an eye movement; electrooculograms were not obtained for technical reasons. All trials were divided based on the amplitude of this positive deflection into those below and above the median (Fig. 5*B*). A significant shift was observed in the "eye-movement" trials in the frontal electrodes only. However, the amplitude of the three main components of the TMS-elicited evoked potentials did not differ in the two types of trials.

DISCUSSION

The results of our study demonstrate that single-pulse TMS *1*) elicits large-amplitude negative scalp potentials 45 ms after the pulse and *2*) induces a highly synchronous oscillation in the 15- to 25-Hz band. In the ensuing discussion, we shall first address methodological issues related to the possible confounding effects of TMS-related auditory and somatosensory stimulation. Discussion of the nature of the observed TMS-elicited scalp potentials and TMS-induced cortical oscillations will follow.

Methodological issues

Immediately after the TMS pulse (<20 ms), a widespread EEG artifact was present in the majority of subjects despite the use of the sample-and-hold circuit. The source of the artifact is unclear; it might be related to the movement of the scalp relative to the cap (as elicited by a direct stimulation of scalp muscles) or, perhaps, to residual current induced in the electrodes. Such an artifact was not observed in the original study by Ilmoniemi and colleagues (1997); in their study, however, a more focal figure-of-eight coil and a bi-phasic pulse were used.

Discharging the TMS coil is accompanied by a loud click and a knocking sensation on the scalp. As shown by Nikouline et al. (1999), the click elicits auditory-evoked potentials (AEP), namely the N1-P2 complex, with the maxima over the central and parietotemporal regions. In the present study, we used 90-dB white noise played through insert earphones to mask the coil-generated click. All subjects indicated that the white noise was sufficient to mask the auditory input. This was confirmed objectively in one subject by recording AEPs to the coil discharging 2 cm above the head; no AEPs were observed. Fur-

thermore, our previous TMS studies with positron emission tomography suggest that white noise is sufficient to prevent significant changes in cerebral blood flow in auditory cortex during TMS (Paus et al. 1997, 1998, 2000); this is not the case without the masking noise (Paus, unpublished observations).

During TMS, the scalp under the coil is stimulated both mechanically and electrically, giving rise to somatosensory input. Such sensations are difficult to abolish short of invasive procedures such as a nerve block. But somatosensory stimulation of the left side of the head would be expected to elicit somatosensory potentials over the right central and parietal regions. This was the case in a control experiment, carried out in one subject (*AS*) in whom we used direct electrical stimulation of the scalp (Fig. 5*D*). In the TMS study, however, somatosensory potentials contralateral to the stimulation site were not observed. Suprathreshold TMS of the motor cortex can also induce somatosensory input through muscle activation and related somatosensory afference. The results of direct electrical stimulation of the right ulnar nerve, which induced muscle activation comparable with that elicited centrally by TMS, show clear differences in amplitude, latency, and scalp distribution of the somatosensory evoked potentials when compared with those elicited by TMS (see Fig. 5*C*). We conclude that the first two components of TMS-elicited potentials (i.e., P30 and N45) are unlikely to have been confounded by muscle-related somatosensory input. Taking into account the average delay between the TMS pulse and the muscle response (about 25 ms), the first somatosensory component (N65) could have contaminated the second TMS-elicited component (N100). But the reanalysis of EEG data using the median-split of TMS-induced EMG response (Fig. 5*A*) suggests that muscle activation did not affect any of the three TMS-elicited potentials.

TMS-elicited scalp potentials

Single-pulse TMS elicited a series of scalp potentials, with a positive wave peaking at 30 ms and two negative waves peaking at 45 and 100 ms, respectively. No evoked potentials were observed beyond the 200-ms postpulse epoch reported in this study. It should be noted, however, that due to a stimulation artifact, the first 20 ms following the pulse were excluded from the analysis. A similar P30/N45/N100 waveform has been observed by Tiitinen et al. (1999) during suprathreshold TMS delivered with a circular coil positioned over the vertex. As the Tiininen et al. study focused on the interaction between TMS and auditory stimulation, the authors did not discuss the possible origin and mechanisms of generation of these potentials. The first question we would like to address here is whether the three potentials reflect a single process. Several characteristics of the N45 component distinguished this potential from the other two components. The N45 amplitude correlated with intensity of TMS, while this was not the case for P30 and N100. The N45 amplitude correlated neither with that of P30 nor with that of N100; on the other hand, the amplitudes of P30 and N100 were correlated. Dipole modeling suggested that the generator of N45 was located in the left central sulcus; no such dipole was obtained for P30 and N100. Finally, paired-pulse TMS reduced the amplitude of N45 (and P30) but not that of N100. Taken together, it seems that different mechanisms may underlie the generation of each of the three potentials elicited by single-pulse TMS of the primary motor cortex, as observed in this study. Several lines of evidence allow us to speculate about the possible nature of the N45 potential. The potential maps (Fig. 2*A*) and the dipole model (Fig. 2*B*) suggested that the cortical generator is located in the primary motor cortex. This possibility is further supported by a recent study of Ashby et al. (1999), who carried out a series of investigations on a patient with cortical myoclonus. One aspect of the study involved direct electrical stimulation of the primary motor cortex and simultaneous electrocorticography (EcoG), both achieved with subdural electrodes placed over the leg area of M1. Single monopolar stimuli applied to the leg area of M1 elicited an initial burst of four positive potentials within the first 10 ms poststimulus, followed by another two positive potentials at 44 and 79 ms; all these potentials were recorded bipolarly between two contacts adjacent to the stimulating electrode. Furthermore, paired-pulse electrical stimulation applied at the same location with 10-ms interpulse interval resulted in the absence of the positive potential expected at about 40 ms after the second pulse. Thus there are two striking similarities between the N45 component elicited in our study by TMS and the cortical potential elicited by direct stimulation of the motor cortex. First, the latency is almost identical in our group of seven subjects (44.9 $\pm$ 0.6 ms, mean $\pm$ SE) to that in the patient (43.9 $\pm$ 0.3 ms). Second, paired-pulse stimulation disrupts the "44-ms" potentials both in the case of TMS and during direct electrical stimulation. Based on these similarities, we offer the following explanation of the N45 genesis. The TMS pulse causes a discharge of neurons in the primary motor cortex; unlike in the Ashby et al. EcoG study, this initial discharge is not observed on EEG due to the stimulation artifacts present in the first 20 ms after the pulse. The initial discharge resets the ongoing rhythmic activity of a local pacemaker, giving rise to the second potential at 45 ms after the pulse; the bigger the initial discharge, the higher the N45 amplitude and the more likely the occurrence of TMS-induced oscillation at the resonant frequency (see *TMS-induced oscillations*).

TMS-induced oscillations

Single-pulse TMS induced oscillations in the beta range in five of seven subjects (Table 1*D*). These oscillations were highly synchronized and lasted for several hundred milliseconds (Fig. 4). Other investigators were able to induce similar oscillatory responses, in different frequency bands, using various stimuli (see Basar 1980 and Bullock 1992 for reviews). In the motor domain, movement typically suppresses the ongoing beta rhythm recorded over the precentral region, hence event-related desynchronization (e.g., Pfurtscheller and Aranibar 1979); a "rebound" of the 20-Hz activity is observed after the movement (e.g., Salmelin and Hari 1994b). As suggested above, the TMS-induced oscillations observed in this study most likely reflect resetting of the oscillators through cortical stimulation. The probability of inducing such rhythms appeared to be related to the intensity of stimulation; the only two subjects with a minimal oscillatory response are those with the lowest stimulation intensity (*AS* and *TP*). The peak-to-peak amplitude of the P30-N45 components of the TMS-elicited scalp potentials was also the lowest in these two subjects.

Furthermore, the 12-ms paired-pulse stimulation not only reduced the amplitude of the P30 and N45 components but also decreased the amplitude of the TMS-induced oscillation. Although these findings point to the role of the stimulated cortex in generating the oscillations, one can only speculate about the physiological mechanisms involved. It is conceivable that the TMS pulse synchronizes spontaneous activity of a population of neurons within the stimulated volume. Alternatively, the pulse activates "idling" neurons that, owing to their membrane properties or intracortical connectivity, begin to oscillate with a 15- to 30-Hz frequency. Nonetheless, this study confirms the propensity of the sensorimotor cortex to oscillate at these frequencies and provides a demonstration of a new approach to investigating these and other cortical rhythms in healthy and disordered human brain.

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