EEG responses to combined somatosensory and transcranial magnetic stimulation

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Abstract

Objectives: To investigate a possible interaction between sensory processing and transcranial magnetic stimulation (TMS), an experimental set-up permitting multichannel EEG measurements was used.

Methods: A somatosensory stimulus was delivered to the right wrist, while single-pulse TMS was applied to the contralateral somatosensory cortex, either concurrent with the somatosensory stimulus or 10 ms after it. A control condition served to mimic the sound of TMS without actually resulting in brain stimulation.

Results: An enhancement of the P25 component of the somatosensory-evoked potential (SEP) was consistently observed for TMS concurrent with somatosensory stimulus. The effect was topographically specific to the EEG recording sites below the TMS coil, i.e. above the somatosensory cortex contralateral to the stimulated peripheral nerve.

Conclusions: The results can be interpreted (1) as an indication of local interaction between the somatosensory-evoked cortical activity and TMS-evoked activity or (2) as support of a relationship between the background EEG and the evoked potential (EP), this relationship being ‘disrupted’ by TMS. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

An electric stimulus applied to the wrist leads to well-defined changes in the EEG, which are referred to as somatosensory-evoked potentials (SEPs). The electrical activity of the brain can also be affected by pulses of transcranial magnetic stimulation (TMS). To investigate a possible interaction between these modes of stimulation, EEG responses to concurrent application of median nerve stimulation and TMS were recorded in the present study. The results, obtained with a new experimental set-up which permits multichannel EEG measurements immediately after TMS (Ilmoniemi et al., 1997), confirm and extend an earlier study by Kujirai et al. (1993). According to these authors, TMS-dependent changes to the SEP are of interest, because TMS can increase perceptual thresholds for somatosensory stimuli (Cohen et al., 1991). In the present study, the interpretation will be widened to take into account the ‘resonance hypothesis’ concerning the generation of evoked potentials (EPs) or, more generally, event-related potentials (ERPs) (Basar, 1980, 1998, 1999).

1.1. Earlier studies concerning the interference between TMS and electrical stimulation of the median nerve

Using a frontal and a parietal EEG electrode, Kujirai et al. (1993) demonstrated an increase in the P25 component of the SEP when an electrical stimulus to the wrist was accompanied by TMS. The increase in the size of the P25 parietal component was maximal when TMS was delivered 10 ms before the median nerve stimulus. However, most probably because of technical limitations, their study did not cover effects of TMS given immediately after median nerve stimulation and did not include topographic SEP mapping. Furthermore, the evidence to rule out the noise produced during stimulator discharges as a factor affecting the SEP was only indirect.

Using electrodes at C4’ and at C3’, Seyal et al. (1993)
reported an enhancement of the N1-P1 amplitude when median nerve stimuli were applied after TMS. This effect was maximal when the median nerve stimulation followed the magnetic pulse after 30–70 ms. While this study provides statistical results for delays between 10 and 150 ms, no data about simultaneous TMS and median nerve stimulation were given.

Neither of these two studies compared the response to TMS combined with SEP stimulus with a synthetic signal obtained by adding responses to TMS alone and to somatosensory stimulation alone.

1.2. TMS–SEP interaction in the framework of the resonance hypothesis of ERP generation

By using an experimental set-up where artefacts due to the stimulator discharge are largely excluded from the EEG measurement (Virtanen et al., 1997), TMS can be used to ‘change the state of electrical brain activity’ immediately before a peripheral stimulus reaches the brain. In particular, TMS can be viewed as a reset of local information processing as neurons are synchronously activated by a strong TMS pulse. This is of interest in the following framework:

Most signal analysis procedures such as EP averaging rely on the assumption that the EP is a ‘signal’ added to the ‘noisy’ ongoing EEG. As an alternative hypothesis, it has been proposed that the EP results from a reorganization of spontaneous EEG activity in terms of amplitude enhancement (Basar, 1972, 1980) (‘resonance hypothesis’) and phase reordering (Sayers et al., 1974).

Several previous studies have provided experimental support for the ‘resonance hypothesis’, using one of the following approaches.

- Single-trial EPs were classified (off-line) with respect to properties of the EEG in a time segment immediately preceding the respective stimuli (Romani et al., 1988; Brandt et al., 1991; Basar, 1988).
- Properties of the EEG served to ‘control’ stimulus delivery, i.e. sensory stimuli were applied only during periods of predefined EEG properties (Rahn and Basar, 1993a,b; Basar et al., 1998).

In short, the approach chosen here was to use TMS as a means to induce ‘uniform’ states of the EEG (‘reset’) and to compare SEPs recorded in this condition with standard SEP measurements. The prediction from the ‘resonance hypothesis’ was that SEP amplitudes would depend on whether or not TMS was applied. If, however, EPs are strictly additive with the ongoing EEG, TMS should not affect EP amplitudes.

2. Methods

Approval for the study was obtained from an ethics committee of the Helsinki University Central Hospital. Seven normal subjects (aged from 22 to 37 years, two females) were investigated after they had given written informed consent. To elicit SEPs, electrical stimuli were applied to the right median nerve at the wrist while the subject sat comfortably in a chair. The stimulus intensity was chosen to be above motor threshold, but not painful. EMG recordings and the observation of twitches served to monitor muscle contractions throughout the experiment.

Single-pulse magnetic stimuli were given using an experimental set-up described earlier (Ilmoniemi et al., 1997). The stimulus intensity and the location of the figure-of-8 coil were chosen as follows. First, a point above the motor cortex was identified where motor EMG responses of the m. abductor digiti minimi of the right hand could be elicited with minimal amplitude (‘motor threshold’; 50% of TMS stimuli resulted in an EMG amplitude of at least 50 μV). From this position, the coil was moved 1.5–2 cm posteriorly in order to place it above the somatosensory cortex (the symmetry plane between the loops being roughly perpendicular to the central sulcus). The intensity was then increased to 110% of the motor threshold. Throughout the experiment, the coil was fixed to a robust frame above the chair where the subject was seated.

To analyze the topography of the SEP, the EEG was recorded with 60 channels mounted on a cap; a forehead reference electrode was used. A special amplifier design served to minimize the artefact caused by TMS (Virtanen et al., 1997). The amplifier bandpass limits were 0.5 and 450 Hz. The data from each channel were digitized continuously at 1450 Hz with a 16 bit AD converter. Artefact removal (by visual inspection) and averaging were done offline.

In order to rule out possible confounding effects of the loud noise produced during the TMS pulse (‘coil click’), the following experimental design was chosen (Tiitinen et al., 1999; Nikouline et al., 1999).

- Condition A, ‘sham TMS’: the TMS coil was held at 2 cm from the subject’s head. In this condition, as opposed to ‘real TMS’ (see below), the stimulator discharge did not cause effective magnetic stimulation, although the coil click was the same. As a rigid piece of plastic was interposed between the coil and the subject’s head, the vibration caused by the click and the consequent bone-conducted increases in the intensity of the auditory stimulus were also mimicked (Nikouline et al., 1999). Sham TMS stimuli were delivered either alone or concurrently with the electrical stimuli.
- Condition B, ‘real TMS, delay 0 ms’: the coil was placed above the somatosensory cortex as described above, in immediate contact with the scalp. TMS stimuli were delivered either alone or concurrently with the electrical stimuli.
- Condition C, ‘real TMS, delay 10 ms’: in 6 out of the 7 subjects, block B was repeated except that TMS was delayed by 10 ms from the median nerve stimulation.

Within each condition, 3 blocks of trials were recorded.
Each block consisted of 120 trials divided into 6 sets of 20 trials. TMS was presented alone (‘TMS’) in two sets, SEP stimuli were presented alone (‘SEP’) in two sets, and TMS was combined with SEP (‘TMS&SEP’) in two sets. In different blocks, these sets were applied in a different sequence to exclude possible effects caused by a particular succession of sets. This design also served to exclude effects of the duration of the experiment. In sum, there were 120 trials of each stimulus type within each of the conditions A, B, and C. Regardless of stimulus type, the interstimulus interval varied randomly between 1.5 and 2.5 s.

In order to identify effects of interaction between TMS and SEP, responses recorded with ‘TMS&SEP’ were compared with the synthetic signal ‘synthTMS+SEP’ computed by adding the responses to ‘TMS’ alone and the responses to ‘SEP’ alone. For further evaluation, difference waveforms were computed by subtracting the ‘synthTMS+SEP’ curves from the (experimentally recorded) ‘TMS&SEP’ curves. For control purposes, this was done for all conditions, i.e. regardless of whether ‘real TMS’ or ‘sham TMS’ was used. Difference waveforms from electrodes near the stimulation site served to define a time window of interest for statistical analysis. The whole cerebral distribution of the difference waveform within this time window was displayed in topographic plots, where a standard MATLAB cubic interpolation routine was chosen.

3. Results

3.1. Comparison between responses to TMS, SEP, and TMS&SEP within condition B (real TMS, delay 0 ms)

Fig. 1 shows a typical example of SEP, TMS, TMS&SEP, and synthTMS+SEP waveforms (subject H.W.). The comparison between the latter two, referring to amplitude enhancements caused by the interaction of TMS and a somatosensory stimulus when delivered simultaneously, shows marked differences in amplitude at the P25 latency and at the subsequent negative deflection. After visual inspection of the curves, the P25 latency range (20–30 ms) was defined as a ‘region of interest’ because, as a result of its short latency, it is least affected by the coil click. The effect described above will be referred to as ‘P25 enhancement’ in the condition TMS&SEP in comparison to synthTMS+SEP.

3.2. Difference between conditions A (sham TMS), B (real TMS, delay 0 ms), and C (real TMS, delay 10 ms) with respect to the difference waveform TMS&SEP minus synthTMS+SEP

Within the ‘region of interest’ (20–30 ms) after somatosensory stimulation, amplitudes of the difference curves ‘TMS&SEP’ minus ‘synthTMS+SEP’ were measured in individual subjects for EEG channel 27 (below the centre of the TMS coil, contralateral to the side of somatosensory stimulation) and channel 31 (opposite to the TMS coil, ipsilateral to the side of somatosensory stimulation). Fig. 2 shows the amplitude of the P25 enhancement in conditions A, B, and C.

The amplitude of the P25 enhancement in channel 27 (contralateral, Fig. 2A) was higher for real TMS than for sham TMS in 6 out of 7 subjects (in one subject, the amplitudes for sham TMS and for real TMS were approximately equal). In the two real TMS conditions (no delay versus 10 ms delay), the amplitude of the P25 enhancement was higher for no delay than for 10 ms delay. This was observed consistently in all the 6 subjects with data for both conditions, the difference being especially marked for 4 of these subjects (ANOVA for (1) sham TMS versus (2) real TMS, delays 0 and 10 ms).

Fig. 2. Amplitudes of the difference curves ‘TMS&SEP’ minus ‘synthTMS+SEP’ in conditions A, B, and C (‘sham TMS’, ‘real TMS, no delay’, and ‘real TMS, 10 ms delay’). Box-and-whisker plots (showing the 5th percentile, 10th percentile, median, 90th percentile and 95th percentile) illustrate the differences between conditions and the distribution within the group of subjects. (Left) ‘Contra’: electrode 27, which was above the somatosensory cortex of the left hemisphere, i.e. contralateral to the site of somatosensory stimulation. (Right) ‘Ipsi’: electrode 31, at the right hemisphere counterpart of position 27, i.e. ipsilateral to the site of somatosensory stimulation.
3.3. Topography of the P25 amplitude enhancement (in condition B)

Fig. 3 illustrates the topographic distribution of the P25 enhancement, measured as the difference between ‘TMS&SEP’ and ‘synthTMS+SEP’ (time window as defined in the previous section). The topographic distribution of the P25 enhancement is shown as the grand average of the spatial maps from all subjects. The amplitude of the P25 enhancement is highest in channels 27 (co-ordinates in Fig. 3A: 4, −5), 28 (5, −5), 37 (4, −6), and 38 (5, −6). All of these channels, contralateral to the side of somatosensory stimulation, are in close proximity to the somatosensory cortex and below the TMS coil.

4. Discussion

The data presented here show that TMS applied concurrently with somatosensory stimulation enhances the P25 amplitude of the SEP. This effect was topographically specific to the somatosensory cortex contralateral to the stimulated side, i.e. the region beneath the TMS coil. While confirming an earlier study by Kujirai et al. (1993), the present study is the first to address the topographic distribution of this effect. The novel experimental set-up permitted a comparison between TMS applied simultaneously with and 10 ms after the somatosensory stimulus. Furthermore, in contrast with earlier studies, the present data are based on a comparison between ‘real TMS’ and a synthetic signal obtained by adding 'SEP alone’ and ‘TMS alone’ to show a specific interaction between the responses to two types of stimuli.

The control stimuli of the present study took into account both the sound of the coil click and the vibration induced during TMS as a factor enhancing the intensity of the ‘coil click’ (via bone conduction) (Nikouline et al., 1999; see also Tiitinen et al., 1999). It is to be mentioned that the present study is focused on an SEP component of short latency (P25), where a significant contribution of the click-evoked response can be ruled out. Two further issues related to the TMS-induced vibration remain to be discussed. (1) The difference between sham TMS and real TMS could be an effect of lower versus higher vibration. This, however, is not a realistic explanation because it would imply that the P25 increase is highest in those subjects where the stimulus intensity was highest (which was not the case). (2) The enhancement of P25 could be an SEP related to coil vibration. This is not plausible either because then the P25 enhancement would have to be highest in the hemisphere contralateral to the coil (Bennett and Jannetta, 1980). To exclude possible effects of a ‘re-afferent’ response to the muscular twitches caused by TMS, no potentials later than the P25 component were evaluated.

4.1. Interaction of somatosensory-evoked and TMS-evoked neural activity

Kujirai et al. (1993) state that it is unlikely that there is an interaction between TMS-induced cortically-evoked muscular activity and the sensory input from the median nerve (movement begins 40 ms after TMS). According to these authors “the fact that the magnetic stimulator had to be placed in a particular position on the scalp for the effect to be observed rules out the possibility that non-specific factors such as the noise produced by the stimulator discharge or local activity in trigeminal nerve afferents were involved”. The present results, in particular the comparison between ‘sham TMS’ and ‘real TMS’, confirm this interpretation.

Kujirai et al. (1993) explain that the TMS-induced P25 enhancement is due to changed excitability of cortical neurons. TMS, they state, could produce a brief period of...
excitation followed by a prolonged inhibition. Hyperpolarization is accompanied by a decrease in transmembrane resistance which in turn increases synaptic currents leading to an increase in P25.

As to the differences between ‘real TMS, no delay’ versus ‘real TMS, 10 ms delay’, an explanation might involve the fact that depending on the delay, part of the interaction may take place at the thalamic level. The data presented here do not permit one to evaluate what part of the effect originates at the thalamus. However, with shorter delays, thalamic interaction is more plausible (TMS reaching the thalamus via fibres connecting thalamus and cortex), whereas with longer delays the cortical level is more plausible (when the neural activation elicited by the somatosensory stimulus reaches the somatosensory cortex). Remarkably, Seyal et al. (1992) found an increase in the perceptual threshold also when applying TMS after somatosensory stimulation. This effect was reported to be most marked when TMS was applied 20–30 ms after stimulation.

It is very unlikely that interaction between TMS-induced activity and the afferent volley takes place at the spinal level. If this were the case, then it would be reasonable to expect corticospinal volleys initiating voluntary movements to modify the earliest SEP components. However, Cohen and Starr (1987) observed movement-induced attenuation only for those SEP components with latencies exceeding 20 ms. In contrast, no attenuation of (subcortical) P14 or (post-central) N20 was observed, i.e. the gating of SEP does not take place below the cortical level.

4.2. TMS–SEP interaction and the resonance hypothesis

A further conceivable explanation of the P25 enhancement starts from the assumption that TMS induces a ‘global yet uniform change’ (‘reset’) of brain electrical activity in the stimulated region. TMS might have ‘disrupted’ the relationship between EEG and EP, thus affecting the EP.

While such a relationship is not taken into account in conventional EP analysis, there is some experimental evidence of spontaneous activity before an external event influencing the response evoked by that event (McDonald, 1964; Rodin et al., 1965; Jasiukaitis and Hakarem, 1988; Pritchard et al., 1985; Romani et al., 1988; Brandt et al., 1991; Jansen and Brandt, 1991; Makeig, 1993; Intriligator and Polich, 1994, 1995; Polich, 1997).

In particular, TMS could interfere with the phase resetting and amplitude enhancement of *spontaneous EEG oscillations* which underlie EP generation according to the ‘resonance hypothesis’ (Basar, 1980, 1998, 1999); the central role of EEG oscillations in this hypothesis links EPs to neuroelectric oscillations as possible correlates of cognitive processes (Gray and Singer, 1987; Gray et al., 1989; Eckhorn et al., 1988; Tallon-Baudry and Bertrand, 1999).

Experimental tests of the resonance hypothesis were done by delivering stimuli only when the EEG fulfilled certain criteria (Rahn and Basar, 1993a,b; Basar et al., 1998). Such selective stimulation enhanced amplitudes of auditory and visual EPs by up to 30%.

4.3. Conclusion

The experimental set-up of the present study, minimizing TMS-induced artefacts in the EEG, served to demonstrate interactions between responses to TMS and a somatosensory stimulus, thus confirming and extending earlier studies. An amplitude enhancement of the P25 component of the SEP was observed, being maximal when ‘real TMS’ was used concurrently with the somatosensory stimulus. There are at least two interpretations of this result. The first focuses on a local interaction between the TMS-induced activity and the afferent volley of neural activation caused by the somatosensory stimulus (this interaction might take place at a cortical or thalamic level), with hyperpolarization of cortical neurons as a possible mechanism. The second points out that the results support a relationship between the spontaneous EEG and the EP. Further studies should decide which of these interpretations – or their combination – is to be preferred.

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