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Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity

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MOTOR and visual cortices of normal volunteers were activated by transcranial magnetic stimulation. The electrical brain activity resulting from the brief electromagnetic pulse was recorded with high-resolution electroencephalography (HR-EEG) and located using inversion algorithms. The stimulation of the left sensorimotor hand area elicited an immediate response at the stimulated site. The activation had spread to adjacent ipsilateral motor areas within 5–10 ms and to homologous regions in the opposite hemisphere within 20 ms. Similar activation patterns were generated by magnetic stimulation of the visual cortex. This new non-invasive method provides direct information about cortical reactivity and area-to-area neuronal connections.

Key words: Connectivity; EEG; Electroencephalography; Interhemispheric transfer; Motor cortex; TMS; Transcallosal connections; Transcranial magnetic stimulation; Visual cortex

Introduction

The intricate patterns of cerebral activity associated with our sensory, motor, and cognitive functions are largely defined by neuronal connectivity. While local connections between neurons are located within the gray matter,[1] fibers in the white matter bridge functionally related cortical areas over long distances directly[2,3] or indirectly.[4] In neural network theories of the brain, connectionist models play a central role.[5] While positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and electroencephalography (EEG) are able to provide maps of the distribution of activity in the brain, they are of little use in determining corticocortical connections. We have developed a tool to evaluate non-invasively cortical reactivity and functional connections between different brain areas.[6] By locating with high-resolution EEG (HR-EEG) the changing pattern of the neuronal activity evoked by transcranial magnetic stimulation (TMS), the initial cortical response reflecting cortical reactivity as well as the spread of activation from the stimulated site to other areas can be determined. This new brain-mapping method appears promising for the study of the functional organization of the human brain.

In TMS,[7,8] a changing magnetic field induces electric currents in the brain, causing depolarization of cellular membranes and thereby neuronal activation. The currently available TMS devices can focus the sub-millisecond pulses on areas of 30 mm in diameter.[9,10] On the other hand, HR-EEG[11,12] enables one to follow sequential cerebral activation with millisecond temporal resolution and with spatial accuracy of about 10 mm when the number of generator sources is small. If no assumption of localized distinct sources can be made, however, the spatial resolution of the EEG is on the same order as the interelectrode distance, i.e., in practice, no better than 3–5 cm. So far, TMS has been limited to observing the brain's motor and behavioral output while conventional evoked-response EEG studies have been confined to using the sensory pathways for stimulating the cortex. The combination of TMS and EEG is free from these limitations: an arbitrary patch of superficial cortex can be stimulated and the resulting responses everywhere in the brain can be monitored. TMS can not, however, be focused in depth.[13] Source localization based on multichannel recordings of the TMS-evoked electric potentials allows, for the first time, one to map non-invasively both intra- and interhemispheric connectivity and to determine transmission times. In previous attempts at combining TMS and EEG, source localization was not possible because the EEG recordings were limited by artefact problems to just 2–3 simultaneous channels.[14,15]

Materials and Methods

Magnetic pulses to the motor and visual cortices were delivered at the rate of 0.8 Hz to four right-handed volunteers (23–34 years old; three males), seated in a chair. The subjects gave informed consent to the study, which was approved by the Ethical Committee of the Department of Radiology of the Helsinki University Central Hospital. The stimulator coil consisted of two coplanar circular 40-mm-diameter wings, each made of 15 turns of copper wire. The figure-of-eight coil was placed against the scalp; its location and orientation were digitized for later reference. The location of the motor cortex was determined by adjusting the position of the stimulating coil until the contralateral small hand muscles gave a response. Stimulus intensity was set slightly below the threshold for evoking motor responses; the peak magnetic flux density at the scalp was then 1.3–1.9 T while the induced electric field in the superficial cortex was of the order of 50 V/m. The same pulse strength was used for stimulation of both motor and visual cortices. Occipital coil location was selected by using external anatomical landmarks. The coil was oriented so that the induced current was in the posterior–anterior direction during the rising phase of the biphasic 320-μs pulse.

The EEG was measured from 20–29 electrodes placed on the scalp according to the International 10-20 system and referred to the nose. The average potential from all recording electrodes was used as the reference for constructing the potential maps. To avoid artefacts in the EEG caused by the TMS pulses that had limited the previous connectivity studies,[14,15] we developed the present EEG system specifically for use with TMS. Low-conductivity small Ag/AgCl-pellet electrodes eliminated possible heating effects.[16] The saturation of the EEG amplifiers during the TMS pulse was avoided by using a sample-and-hold circuit that pinned the amplifier output to a constant level during the pulse. The amplifiers recovered in just 100 μs after the end of the magnetic pulse. The data were sampled at the rate of 3 kHz and digitally low-pass filtered at 250 Hz. For each averaged EEG waveform, about 150 responses were recorded.

The distribution of neuronal activity as a function of time was estimated by computing the primary current distribution $\mathbf{J}^p(\mathbf{r})$ that had the smallest overall amplitude (minimum norm, $\sqrt{\int |\mathbf{J}^p(\mathbf{r})|^2 dv}$) among those source current distributions that are compatible with the data. CURRY software (Philips GmbH, Germany) was used for the surface reconstruction of the cortex (Fig. 1) and for the minimum-norm estimation[17] of the activity. A realistically shaped head model based on MRI data was used in the calculations.

Results

Figure 1a shows the evolution of cortical activation following the magnetic stimulation of the hand representation area in the left motor cortex. An immediate, localized, very strong response was apparent at 3 ms post-stimulus. Activation at the adjacent ipsilateral motor and premotor areas, with dense corticocortical interconnections with the stimulated area[3,18] was observed during the next few milliseconds. Furthermore, a clear activation of the contralateral homologous cortical areas, probably transmitted by transcallosal connections, emerged within 20 ms post-stimulus, in agreement with previous brain stimulation,[19,20] cognitive,[21] and epilepsy[22] studies.

As a demonstration that the responses measured do not result from peripheral sensory activation due to motor activity, we also stimulated the visual cortex, and observed a similar time-course of activation to that resulting from motor cortex stimulation. Figure 1b shows the activation pattern resulting from left occipital stimulation; after immediate ipsilateral activation, there was a contralateral response at about 20 ms. Later, in both visual and motor modalities, the field patterns appeared to be generated by multiple brain areas, including the auditory cortex, which was activated by the sound accompanying TMS pulse delivery.

The strongest EEG activity immediately after stimulation was observed below the center of the figure-of-eight TMS coil, i.e., at the site of the strongest induced current flow. In all subjects examined and for both motor and visual cortex stimulation, neuronal activation during the first 5 ms post-stimulus produced a current flow in the anterior–posterior direction; at 6–7 ms, the direction of the current was reversed (Figs 1, 2).

Figure 2 displays the temporal evolution of the EEG potential map in another subject during the first 30 ms after left-hemisphere hand-area stimulation. Patterns of cortical activation similar to those shown in Fig. 1a are evident in these maps. At 3 and 24 ms post-stimulus, the field maps could

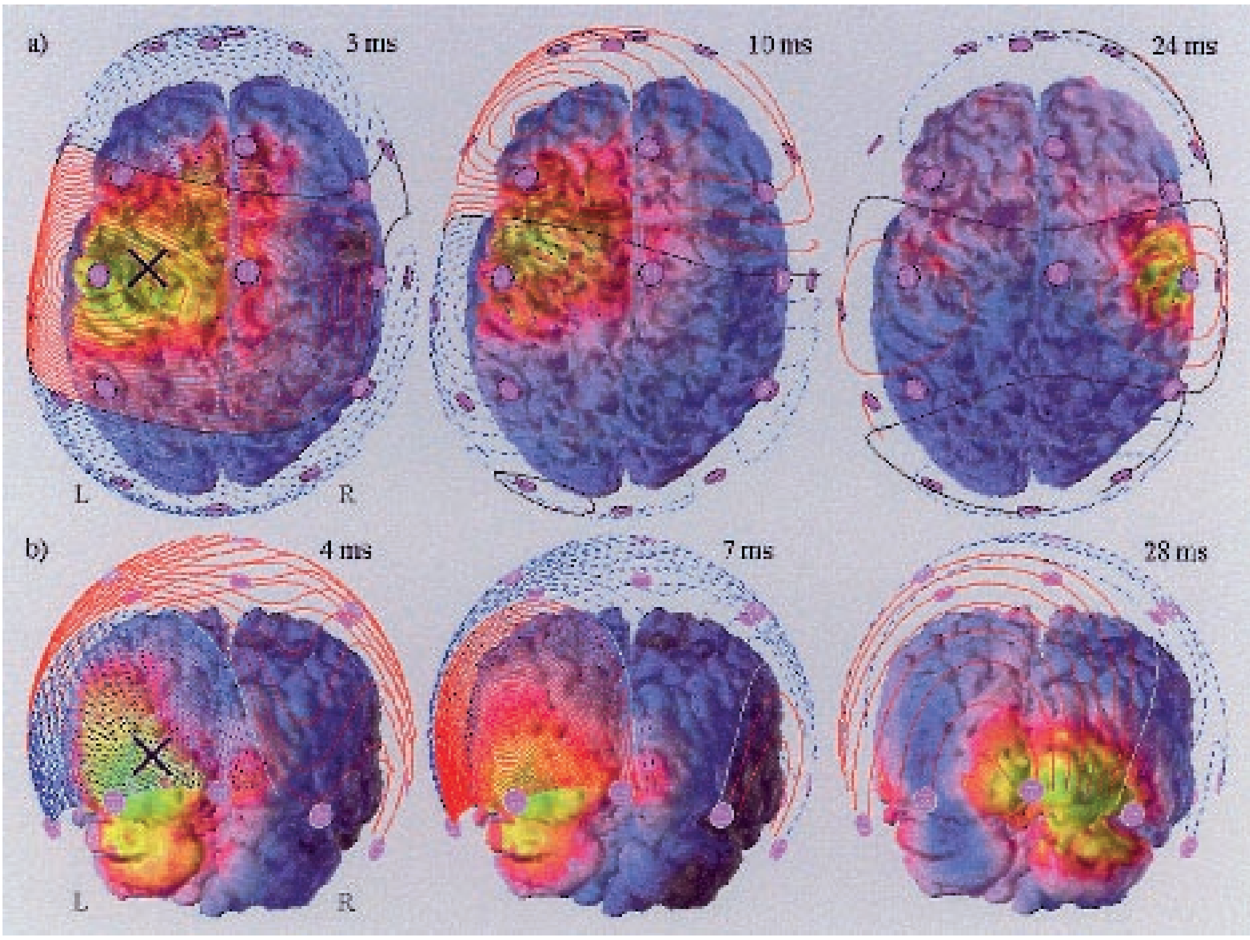

FIG. 1 Activation maps based on TMS-evoked averaged EEG responses, subject JA. Minimum-norm estimates of the cortical activity are shown as color maps drawn on three-dimensional magnetic resonance images of the cortical surface of the same subject. The magnetic resonance images (MRIs) were acquired with a Siemens Vision 1.5-T system (Siemens, Germany) using a set of 1-mm-thick sagittal MPRAGE images (TR 9.7 ms, TE 4 ms, TI 20 ms, flip angle 10°). In order to register the EEG data with the 3D MRI images, electrode and coil locations with respect to head landmarks were determined with a 3D digitizer pen (Polhemus, USA). Superimposed, the EEG is displayed as contour maps, with red lines indicating positive potential. The TMS coil position is indicated with a cross. L and R indicate the left and right hemispheres, respectively. (**a**) The response to left motor cortex stimulation. At latencies of 3 and 10 ms, the ipsilateral hemisphere shows prominent activation; at 24 ms, the contralateral activity dominates (between 10 and 24 ms, the two hemispheres showed simultaneous strong activation). The EEG contour spacing is 1 μV. (**b**) The response to visual-cortex TMS at 4, 7 and 28 ms post-stimulus; the contour spacing is 2 μV.

be explained by localized dipole sources (depicted by the arrows) in ipsilateral and contralateral hand representation areas, respectively.

Discussion

We have reported here, for the first time, the mapping and localization of neuronal responses to TMS stimulation of motor and visual cortices. TMS can be targeted to arbitrary areas of the (superficial) cortex, whereas activation through peripheral stimulation is limited to specific sensory pathways. Following stimulation of the motor cortex, we observed the spreading of neuronal activation from motor to premotor to contralateral and then to parietal areas (see Fig. 2, last panel). Stimulation of visual areas, in turn, caused neuronal population responses first ipsilaterally and then contralaterally in the occipital lobe.

Paus *et al.*[23] recently used PET to record changes in cerebral blood flow resulting from TMS, demonstrating that neuronal connectivity can be studied by combined PET and TMS. Corticocortical functional relationships have also been studied by determining covariances between EEG signals recorded from different scalp sites during cognitive tasks.[18] While the hemodynamic responses observed with PET are an indirect and delayed reflection of neuronal activity, EEG provides direct and exquisitely timed information about TMS-evoked activity. HR-EEG makes it possible to locate the responses with an accuracy of 1–2 cm and to follow the spread of activity

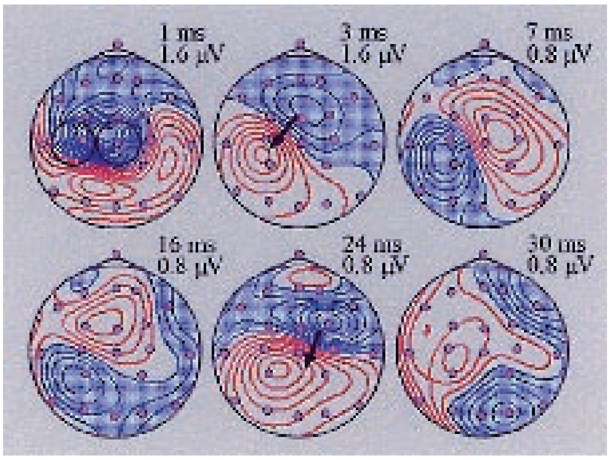

FIG. 2 The evolution of the EEG potential maps during the first 30 ms after the stimulation of the hand area in the left hemisphere, subject SK. The dots denote the recording electrodes. The black circles in the upper left panel depict the two wings of the TMS coil. The contour spacing is indicated next to each map; the red and blue lines correspond to positive and negative potentials with respect to the average potential, respectively. The early ipsilateral (3 ms) and contralateral (24 ms) field patterns can be explained by equivalent current dipoles (ECDs) at the left and right sensorimotor areas, respectively. ECD locations were determined from the EEG data with the BESA software (MEGIS Software GmbH, Munich, Germany) using a spherical head model. The ECD is the current dipole that best explains the measured electric potentials at a given time. The arrows show the locations and orientations of the ECDs. At 3 ms the dipole moment was 14 nAm; at 24 ms it was 3.6 nAm.

with millisecond temporal resolution. The timing information may also help in distinguishing direct corticocortical activation from delayed responses transmitted, e.g. via the thalamus or via other brain structures, since indirect transit times can be expected to be longer than direct ones.

Since the induced field can not be focused in depth, only cortical areas near the outer surface of the brain can be selectively stimulated with TMS. However, the ability of the EEG to detect signals from deep structures allows one to study connectivity from cortex to subcortical nuclei as well, although the present study demonstrated cortex-to-cortex connectivity measures only.

The interpretation of TMS-evoked EEG data requires one to know which parts of the brain were stimulated. Since the most superficial subcortical nuclei, the basal ganglia, are roughly half-way from the surface of the brain towards the center, it appears, because of the strong dependence of the field strength on depth, that only the superficial cortex or possibly the white matter immediately below it is activated.

TMS is usually targeted using motor or other responses as indicators of stimulus locations or else, anatomical external landmarks are used. In the motor-cortex stimulation, we applied the former method, in the occipital-cortex stimulation, the latter. Improved spatial resolution in stimulating the cortex, accurate targeting, and the possibility for rapid scanning will be achieved with forthcoming TMS arrays.[9] Simultaneously, the resolution of EEG mapping will improve with the use of denser electrode arrays.[25]

Conclusion

Connections between different areas of the brain can now be mapped by stimulating magnetically one part of the cortex and then observing and modelling the electric activation of other parts. In addition, the immediate cortical response offers a measure of cortical reactivity. The combination of TMS and high-resolution EEG provides a new, exceptionally potent non-invasive tool for basic neuroscience and clinical diagnosis, including the assessment of cortico-cortical and interhemispheric functional connections in patients suffering from neurodegenerative diseases or head injuries.

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