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Imaging the brain before, during, and after transcranial magnetic stimulation

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Abstract

This article provides a brief overview of current trends in combining neuroimaging and transcranial magnetic stimulation (TMS). First, I outline the utility of magnetic-resonance imaging (MRI) and frameless stereotaxy for planning, monitoring and documenting the location of the TMS coil relative to the subject's brain. Second, I describe two novel methods, based on the combination of TMS with positron emission tomography (PET) or with electroencephalography (EEG), for the assessment of connectivity and excitability of the human cerebral cortex. Finally, I point out the utility of PET and MRI for evaluating possible long-term effects of repetitive TMS. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: TMS; PET; MRI; fMRI; Frameless stereotaxy

1. Introduction

In the last two decades, we have witnessed the emergence of two powerful tools for investigating brain mechanisms of behaviour: functional neuroimaging and transcranial magnetic stimulation (TMS), the former capable of measuring and the latter of changing activity in the human brain. Until recently, these two methodological approaches lived somewhat independent lives. In this article, I provide an overview of the potential that lies in combining TMS with brain imaging. Several examples will be used to illustrate that such a combination can be useful in three principal ways: (1) imaging the brain before TMS, to identify and target the site of stimulation, (2) imaging the brain during TMS, to assess cortical connectivity and excitability, and (3) imaging the brain after TMS, to evaluate possible long-term effects of TMS.

2. Imaging the brain before TMS

In neuropsychology, the classical paradigm is that of studying the effects of brain lesions on behaviour. With TMS, we can apply this paradigm in spatially and temporally restricted fashion to healthy volunteers. The spatial extent of the effective stimulation depends on the coil design. Using a three-layer (scalp, skull, cortex) spherical model of the head, Roth et al. [34] calculated that, in the case of a figure-eight coil, the magnitude of the induced electric field drops to about 75% of the peak field within 10 mm and thus affects about 600 mm^2 of the brain tissue located under the coil. The duration of the effect depends on the stimulation mode. In single-pulse TMS studies, the duration of the magnetic stimulus is less than 1 ms, but its neurophysiological effects in the motor system may last up to 100 ms. In repetitive TMS experiments, magnetic stimuli are delivered in trains with a frequency from 1 to 25 Hz and a duration varying from hundreds of milliseconds to several seconds. The interfering effects of such repetitive TMS clearly last throughout the stimulation; the presence and duration of possible after-effects is not known (but see TMS effects on mood and depression [7–9, 23, 24].

Several neuropsychological studies have already been carried out that used either single-pulse TMS [2, 11, 14, 17–19, 31, 35, 38] or repetitive TMS [12, 14, 16, 20, 22] to interfere with neuronal activity under the coil. In these and similar studies, the site of stimulation is most often determined in reference to the location of the primary motor cortex (M1) or to scalp locations based on the International 10–20 EEG System. The use of a brain-based coordinate system provides, however, a more direct and universal way to communicate the position of the coil. In the next section, I will describe several approaches that allow the investigator to define the coil position and,

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by extrapolation, that of the stimulation site relative to a magnetic-resonance image (MRI) of the subject's brain.

2.1. Structural MRI and frameless stereotaxy

The first step in planning a TMS study is the acquisition of a high-resolution T_1-weighted image of the subject's brain; this can be accomplished quickly on any standard MR system. For example, we use a 10-min scanning protocol to collect 160 contiguous T_1-weighted 1-mm thick sagittal slices (fast-field 3-D acquisition mode; $T_R = 18$ ms, $T_E = 10$ ms, flip angle $= 30^\circ$). With the subject out of the scanner, the next step involves co-registration of the subject's MRI with the actual position of his/her head. The MRI-to-head co-registration can be carried out either with a fiducial frame attached to the subject's head or without a frame using anatomical landmarks visible on the head's surface, i.e. with frameless stereotaxy.

The fiducial-frame approach was used by Singh et al. [37] who scanned their subjects wearing a dental bite-bar with holes filed with an MR-contrast marker (vitamin oil). The same bite-bar based coordinate system was subsequently used to reference coil locations marked during the TMS experiment on a closely fitting skullcap. The *X*, *Y* and *Z* coordinates of the coil locations were measured with a digitising pen (Polhemus Isotrak System, Kaiser Aerospace Inc.) and projected onto the cortical surface following a co-registration of the actual bite-bar fiducial points with their corresponding MR-images.

Instead of the fiducial frame, the frameless-stereotaxy approach uses a set of anatomical landmarks, such as the bridge of the nose and the tragus of the ear, that are visible on both the subject's MRI and on his/her head [29]. The 3-D location of the landmark is again measured with a digitising pen using an RF-based (e.g. Polhemus Isotrak), mechanical (e.g. Surgeon Arm, FARO Technologies; Fig. 1), or optical (e.g. Polaris) tracking system. The accuracy of the frameless stereotaxy is slightly inferior to that based on a fiducial frame and varies between 4 and 8 mm [45]. It is important to note, however, that this approach allows real-time monitoring of coil position without restraining the subject's head during a TMS experiment. This is achieved by tracking simultaneously the movement of two objects: the coil and the head [5]. Several commercial optical-tracking systems can be used for this purpose: for example the Polaris System by Northern Digital Inc., the Optical Tracking System by Radionics Inc., and the Pixsys by IGT Inc. The optical-tracking systems use a camera to measure the 3-D locations of infra-red LEDs attached on the objects of interest, i.e. the coil and the subject's head in the case of TMS experiments. An important feature of these systems *vis-à-vis* TMS is the possibility of tracking the 3-D orientation of the coil, which is achieved by attaching several LEDs to the coil. Systems based on the location of radio-frequency (RF) waves, such as the Polhemus Isotrak, are not suitable for the on-line monitoring of the coil and head position due to the interfering effects of metallic objects with RF detection.

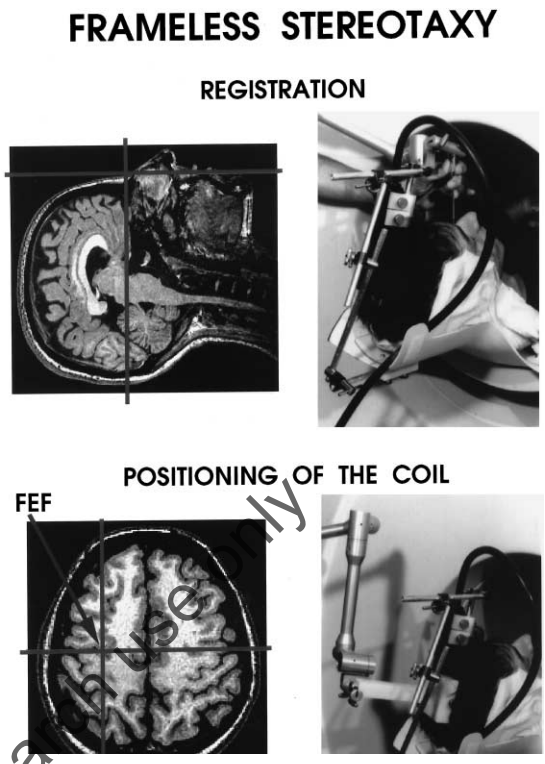

Fig. 1. The top of the figure depicts the process of registering the subject's head with the corresponding magnetic-resonance (MR) image. A computer-linked probe is touching the bridge of the nose (right); the matching location is highlighted by a cross-hair on the MR image (left). The bottom of the figure shows a location targeted by TMS in one of our studies, namely the left frontal eye-field, FEF (left), and the probe–coil interface used to position the coil over this location (right). (1) Arm of the frameless-stereotaxy unit; (2) probe inside the interface; (3) coil inside the interface. Reprinted with permission from Journal of Neuroscience 1997;17:3178–84 [25].

The optical-tracking systems provide an ideal platform for (1) positioning coil before experiments begin, (2) monitoring coil/head movement during the experiment, and (3) plotting the effective stimulation sites on the cortical surface. Until scaled-down versions of such systems are made available for research purposes, however, the less expensive RF-based systems would provide a reasonable alternative for a post-hoc documentation of the coil position relative to an MR image of the subject's brain.

2.2. Frameless stereotaxy and functional MRI

The gross anatomy of the cerebral cortex can serve as a reference system when planning a TMS experiment. But the correlation between the sulcal anatomy and the functional subdivisions of the cortex is not perfect. For example, the frontal eye-field (FEF) is usually located along the precentral sulcus and/or at the junction of

the precentral and the superior frontal sulci [25]. This structure–function relationship, however, is probabilistic in nature and sensitive to slight variations in task parameters, such as saccade amplitude. Localization of the target region could be improved by employing functional-imaging techniques in the planning stage. For example, a functional MRI (fMRI) can be utilized to determine the exact location of the FEF during the execution of small-amplitude horizontal saccades. This information can then guide positioning of the TMS coil with frameless stereotaxy over such an fMRI-defined FEF. We have recently used this approach in a study of the primary motor cortex [27]. The subjects were first scanned with an fMRI during the execution of finger-to-thumb opposition movements. The peak of statistically significant increase in the BOLD signal was identified in each subject and superimposed on the structural image of his/her brain. At the beginning of the subsequent PET session, we used frameless stereotaxy to move the coil over the head until the center of the coil and the fMRI peak were aligned (Fig. 2). Other investigators used co-registered fMRI or PET and TMS-derived datasets when comparing the localization of the human M1 with these different techniques [32, 43].

3. Imaging the brain during TMS

While stimulating the brain with TMS, we can measure central effects of this stimulation with a variety of methods. Several early studies employed single-photon emission computerized tomography (SPECT) to quantify changes in brain perfusion during TMS [4, 36]. More recently, we have combined TMS and positron emission tomography (PET) to study connectivity of the human cerebral cortex [26]. In this and similar studies [6, 27, 28], TMS is applied while changes in regional cerebral blood-flow (rCBF) are measured with PET. Distal effects of focal stimulation are thought to reflect connectivity of the stimulated region, while the local effects may indicate the level of cortical excitability at the site of stimulation.

Several technical issues need to be attended to in combined TMS/PET experiments. First of all, the strong (1.5–2.2 T), albeit brief (200 μs), coil-generated magnetic field can affect photomultipliers and the related electronic circuits housed about 20 cm away from the subject's head in the gantry of the PET scanner. Even though the field falls off quickly with distance, photomultipliers are sensitive to the interfering effects of magnetic fields as small as 10^{-4} T. Using a single-detector assembly and a figure-eight coil, positioned 19 cm from the photomultipliers, we examined such possible effects and showed that operating the coil even at 40% of the maximum output of the stimulator (High-Speed Cadwell Stimulator) causes serious distortions in the crystal identification matrix [26, 40]. We were able to prevent these distortions by placing four sheets of well-grounded mu-metal between the coil and the PET detector. The price paid for this, however, is the attenuation of the γ-rays and the resulting decrease in the number of detected coincidence counts. Our observation of the coil-induced artifacts seems to be at odds with the report by Fox et al. [6] who did not observe any significant differences between TMS-on and TMS-off images of a line [18] F phantom. But these authors arranged the stimulating coil so that the field maximum was about parallel with the scanner's axis, thus avoiding possible interference of the magnetic field with identification of coincidence counts. This arrangement, however, is not possible in all scanners and it also limits the number of possible coil positions and orientations. The second important issue is that of possible movement of the coil relative to the subject's head and the effect of such a misalignment on attenuation corrections. Each PET session begins with a transmission scan that provides information about the location and density of various objects located between the brain, i.e. the source of γ-rays in subsequent emission scans, and the PET detectors. In the combined TMS/PET studies, the coil happens to be the single most attenuating object. Any movement of the coil or the head after the transmission scan will result in an incorrect application of the attenuation corrections when calculating the distribution of counts measured in emission scans [41]. Thus, false positive areas of significant differences in rCBF could emerge in cases where a movement occurred between the TMS-on and TMS-off scans. Turkington et al. [41] suggest that this effect would be limited to regions close (<20 mm) to the coil. Nonetheless, one should still attempt to prevent such a possible artifact. The simplest solution is to orientate the gantry of the scanner so that its axis is parallel with that of the coil and the coil is outside the field-of-view [6]. Besides the fact that not all scanners have a moveable gantry, this solution can again be used only for a few coil locations and orientations. A more flexible alternative would require tracking of the head and coil location throughout the PET sessions using, for example, an optical-tracking system and re-calculating the attenuation corrections when a movement is detected [30, 38]. Besides these two technical issues, investigators should also attend to the potential confounding effects of factors such as the coil-generated noise and scalp sensations, as well as possible behavioural effects of suprathreshold TMS.

Electroencephalogram (EEG) is yet another variable that can be recorded during TMS. The high temporal resolution of EEG affords unique insights into the speed of neuronal conduction within and between the two hemispheres. Cracco, Amassian and their colleagues were the first to combine TMS with EEG in their studies of transcallosal and fronto-cerebellar responses [1, 3]. Ilmoniemi et al. [13] perfected this technique by combining TMS with a 60-channel EEG system; they observed clear trans-

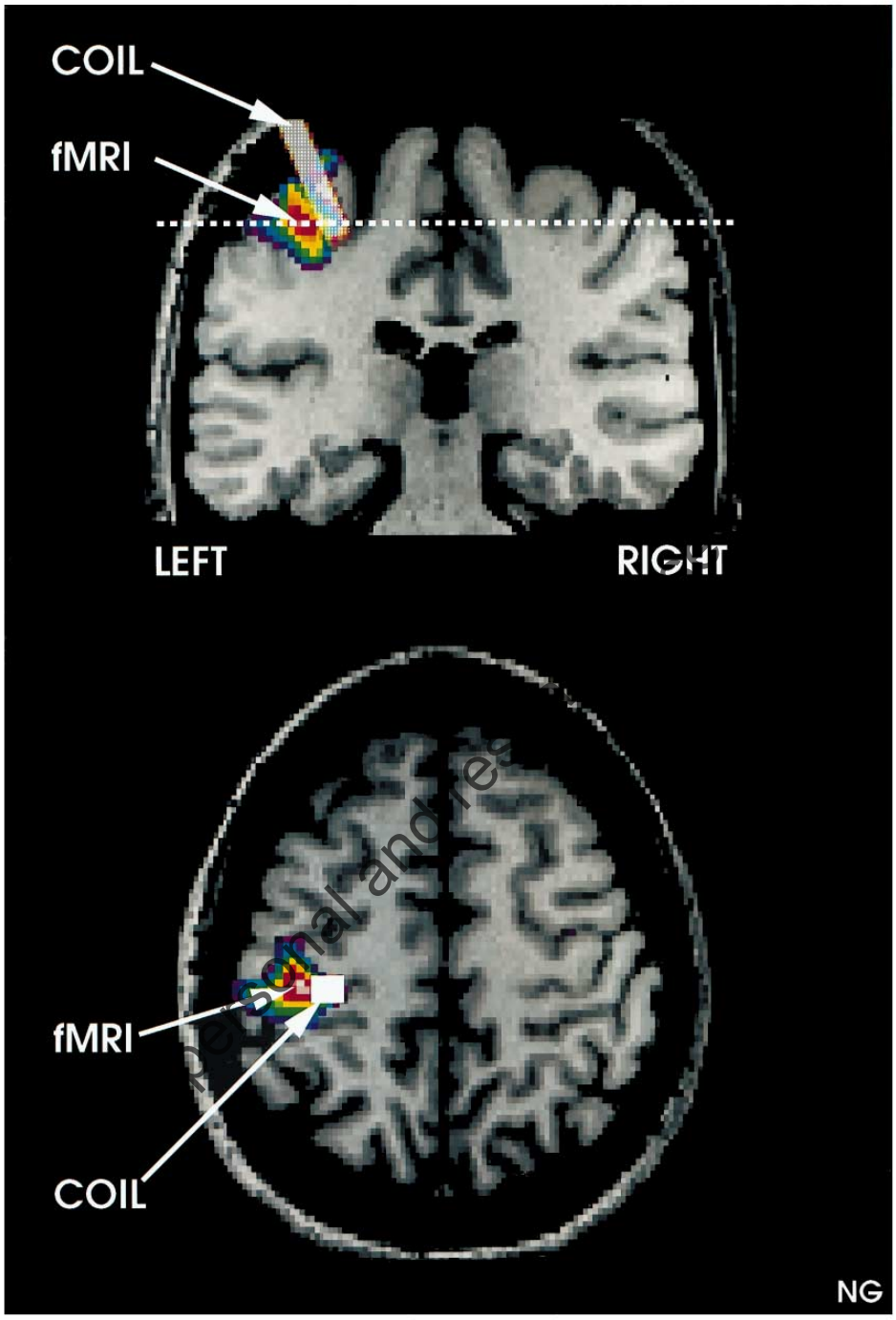

Fig. 2. In the planning phase for a combined TMS/PET study [26], we first identified the left primary motor cortex by acquiring functional magnetic-resonance images (fMRI) during the performance of finger-to-thumb movements with the right hand. The fMRI 'peak' was superimposed on a structural MRI of the same subject; it is marked as the colour-coded region on the coronal (top) and the axial (bottom) slice through the MRI. With the aid of frameless stereotaxy, the centre of the TMS coil was then positioned over this fMRI peak. fMRI, the peak increase in fMRI (bold) signal during finger movements; COIL, a virtual rod projected from the centre of the TMS coil. The actual location of the coil over the subject's head was determined from a transmission scan obtained during the PET session.

callosal EEG responses to magnetic stimulation of the primary motor and visual cortex. To prevent the saturation of EEG amplifiers by the magnetic pulse, these authors designed a sample-and-hold circuit that pins the amplifier output to a constant level during the pulse. The amplifiers recover within 1 ms after the pulse, thus allowing the investigators to measure immediate TMS-induced changes in EEG recorded from electrodes

located directly under the coil. The overheating of the electrodes placed close to the coil [33] is prevented by making the electrodes from low-conductivity material (purified silver with Ag/AgCl coating [42]) and by cutting a slit in the electrode to interrupt eddy currents. We have recently used the Ilmoniemi et al. [13] EEG system in combination with the Cadwell MES-10 stimulator and noted an artifact lasting for about 0.8 s following the pulse. This artifact was caused by a current passing through the coil during the re-charging of the Cadwell stimulator, which has been subsequently re-designed to eliminated this artifact (J. Cadwell, pers. comm.).

Overall, I believe that measuring brain activity during single-pulse or repetitive TMS will become an important tool for investigating cortical connectivity and excitability in the healthy and disordered human brain. For example, we may soon be able to explore possible modifications of connectivity and/or excitability in relation to motor and sensory learning, reorganization of the human brain following injury, possible abnormalities of connectivity in patients with schizophrenia, and normal development of connections in childhood and adolescence. Some of these goals will be better achieved with PET, others with EEG.

4. Imaging the brain after TMS

Very little is known about the long-term effects of repetitive TMS (rTMS). At the cognitive level, it seems that a single session of suprathreshold rTMS does not interfere with performance on such tasks as story recall, word fluency or naming [21]. A slight facilitation of the finger-tapping rate and/or delayed recall of a story was observed 1–2 h after rTMS session in some subjects under certain stimulation conditions [44]. TMS of the left and right frontal cortex was shown to change differentially the subjects' mood when assessed immediately after an rTMS session [8, 23]. Moreover, several studies have now reported beneficial effects of several sessions of rTMS on depression [7, 9, 24] and obsessive–compulsive disorders [10]. To provide a solid rationale for potential therapeutic use, it is indeed critical to determine what mediates such long-term effects of rTMS. Imaging the brain before and after rTMS can clearly contribute in this respect. For example, George et al. [7] observed a normalization of a decreased glucose metabolism following rTMS in one patient. In addition to providing data on changes in brain metabolism, PET can also be used to quantify possible TMS-induced (regional) changes in the enzymatic activity of different neurotransmitter systems and in receptor occupancy.

5. Conclusion

Transcranial magnetic stimulation is a non-invasive tool for manipulating neuronal activity in the human brain. Functional brain imaging provides a variety of ways to measure the effects of such manipulation, while structural imaging produces a spatial frame-of-reference for both. Thus, combination of brain imaging and TMS should further our understanding of brain–behaviour relationships and the potential of rTMS as a therapeutic tool.

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