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Transcranial Magnetic Stimulation During PET: Reaching and Verifying the Target Site

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Abstract: Transcranial magnetic stimulation (TMS) during positron emission tomography (PET) is a novel technique for in vivo measurements of connectivity and excitability of the human cerebral cortex. Here we describe tools that allow investigators to position the stimulating coil over a target region and to verify the actual position of the coil after the study. The former is achieved by coregistering the head of the subject with an MR image of his/her brain using frameless stereotaxy. The latter is accomplished by identifying the coil on a transmission scan and coregistering it, e.g., with a model of the electrical field induced in the brain. *Hum. Brain Mapping 6:399–402, 1998.*

Key words: TMS; PET; connectivity; cerebral cortex; registration; frameless stereotaxy

INTRODUCTION

Rapid switching of a strong magnetic field induces electrical current in nearby conductors. Using a coil placed on a subject's head, such a time-varying magnetic field can be used to stimulate the underlying cortical tissue. Since the magnetic field drops quickly with distance, a reasonably focal cortical stimulation can be achieved with appropriately designed coils [Cohen et al., 1990]. The development of transcranial magnetic stimulation (TMS) thus provided clinicians and neuroscientists with a unique tool for noninvasive manipulation of neuronal activity in the human cerebral cortex [Hallett and Cohen, 1989; Murray, 1992; Cracco et al., 1993].

The effects of TMS are typically measured as changes on an electromyogram, when applied over the motor cortex [e.g., Brasil-Neto et al., 1992; Mills et al., 1992; Priori et al., 1994], or as changes in perceptual or other cognitive processes, when sensory [e.g., Miller et al., 1996; Seyal et al., 1997] and associative [e.g., Hotson et al., 1994; Müri et al., 1994; Pascual-Leone et al., 1991, 1994] cortices are stimulated. More recently, we combined TMS with positron emission tomography (PET) to study connectivity of the human cerebral cortex [Paus et al., 1997]. In this and similar studies [Fox et al., 1997; Paus et al., 1998], TMS was applied while changes in regional cerebral blood flow (rCBF) were measured with PET. Distal effects of focal stimulation are thought to reflect connectivity of the stimulated region, while local effects may indicate the level of cortical excitability at the site of stimulation.

In combined TMS/PET experiments, the location of a target site is critical. Connectivity and excitability of the cerebral cortex vary over short distances, and error in the localization of a target site can therefore compromise interpretation of the results. Here, we provide a

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brief overview of the approaches available for 1) positioning the coil to reach the target site, and 2) verifying coil position during a PET study.

POSITIONING THE COIL

In the past, investigators most often determined the coil location in reference to the location of the primary motor cortex (M1) or scalp locations based on the International 10–20 EEG system. While the first approach is valid when studying the connectivity of M1, it is of limited value when M1 is used as an ''anchor'' for localizing other cortical regions. Brains differ in overall size and gross cortical anatomy, rendering absolute distances between two cortical sites variable across individuals. The same applies for the exact relationship between scalp locations (e.g., P3 electrode site) and cortical sites (e.g., middle section of the left intraparietal sulcus). A coordinate system based on a magnetic resonance image (MRI) of the subject's brain has the advantage of providing a direct structural reference for the stimulation of any cortical site. Furthermore, such an MR-based system allows the investigator to express the location of the stimulation site in standardized stereotaxic coordinates [Talairach and Tournoux, 1988] and to use X, Y, and Z coordinates of a peak observed in a previous activation study to aim the TMS coil at this location during a TMS/PET experiment [Paus et al., 1997].

Once an MR image of the subject's brain is acquired, the next step involves coregistration of the subject's MRI with the actual position of his/her head. This procedure can be carried out either with the aid of a fiducial frame attached to the subject's head [e.g., Singh et al., 1997] or without a frame, using anatomical landmarks visible on the head's surface, i.e., with frameless stereotaxy [Ettinger et al., 1996; Paus et al., 1997]. Frameless stereotaxy uses a set of landmarks, such as the bridge of the nose and the tragus of the ear, that are visible on both the subject's MRI and his/her head [Peters et al., 1996]. The three-dimensional (3-D) location of the landmark is measured with radiofrequency, mechanical, or optical-tracking systems. The accuracy of frameless stereotaxy is slightly inferior to that based on a fiducial frame, and varies between 4–8 mm [Zinreich et al., 1993].

In addition to the initial positioning of the coil, optical tracking systems allow for real-time monitoring of coil position throughout the session. In applications not requiring immobilization of the head, these systems can also be used to track the movement of two objects, i.e., the coil and the head, simultaneously, thus updating the coil position relative to the head [Ettinger et al., 1996]. Several commercial optical-tracking systems can be used for this purpose: 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 infrared LEDs attached to 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. It is important to note that systems based on the location of radiofrequency (RF) waves, such as the Polhemus Isotrak, are not suitable for the on-line monitoring of the coil position, nor for use in a PET scanner due to the interfering effects of metallic objects with RF detection.

VERIFYING THE COIL LOCATION

Frameless stereotaxy allows the investigator to align the center of a figure-eight coil with the target site and to orient the plane of the coil relative, e.g., tangential, to the cortical surface. Even under ideal circumstances, however, accuracy of the frameless-stereotaxy approach is on the order of several millimeters. Using the system in the limited space of the PET scanner may further diminish the successful alignment of the coil with the target site. It is therefore desirable to verify the actual position of the coil achieved during a given PET study. For this purpose, the investigator can take advantage of a transmission scan acquired before the first emission scan.

A transmission scan provides a 3-D image of all dense objects in the scanner's field of view, including the coil or its parts (Fig. 1A), with a spatial resolution of about 2 mm for the CTI/Siemens HR+ tomograph. Barring the movement of the head between the transmission and the subsequent emission scans, one can evaluate the location of the coil on the emission scan and the coregistered MR scan in native space. In addition, the transmission volume containing the coil can also be transferred to standardized stereotaxic space and the coil location defined in X, Y, and Z coordinates.

In order to localize the stimulating magnetic field and/or the modelled electrical field on the cortical surface, we can register the coil visible on the transmission scan with field volumes. In an intermediate step, the coil is coregistered with an X-ray of the entire coil. The transmission volume is displayed so that the display plane passes through the plane of the coil, and coordinates of several points selected around the circumference of each coil are recorded (Fig. 1B). Homologous points are then chosen in the volume

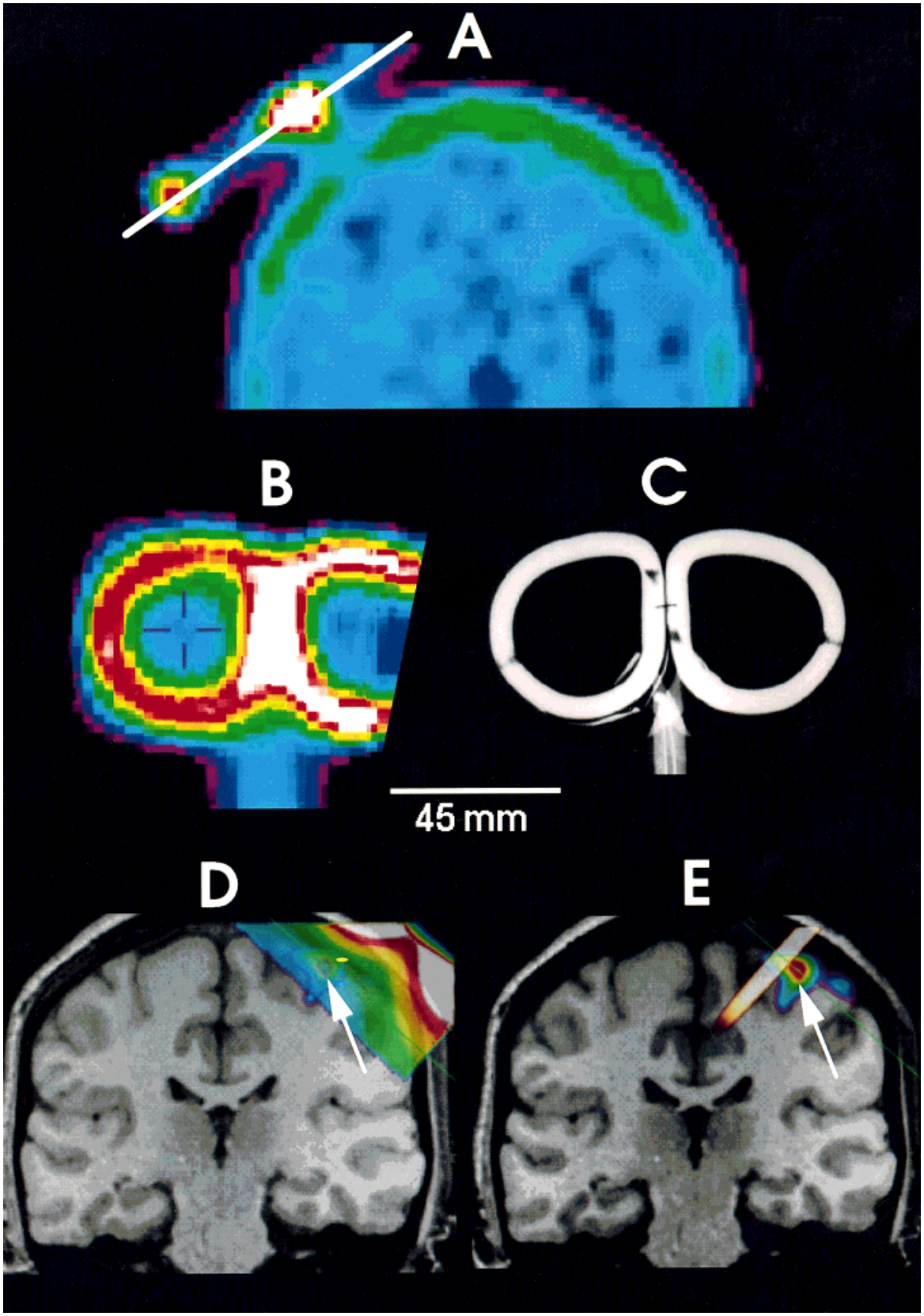

Figure 1.

The use of a transmission scan for verifying position of the TMS coil during PET experiments. **A:** Transmission scan, showing the TMS coil placed over the subject's head. **B:** Transmission scan with the viewing plane through the plane of the stimulation coil. **C:** Planar X-ray image of the stimulation coil. **D:** Modelled electric field merged with structural and functional MRI. Arrow indicates location of right M1, as determined in functional MRI session. **E:** Rod orthogonal to the plane of the stimulation coil merged with structural and functional MRI. Arrow indicates location of right M1, as determined in functional MRI session.

containing the X-ray image of the coil (Fig. 1C). A transformation matrix is then calculated that minimizes the difference between the two sets of registration points. This coil-to-coil transform can be easily combined with PET-to-MRI and MRI-to-Talairach transformation matrices. Having the full coil registered with the transmission image of the coil allows us to merge various other coil-derived volumes with the PET and MRI volumes, including the modelled electric field (Fig. 1D) or a volume containing a straight rod orthogonal to the plane of the coil and projecting from the center of the figure-eight coil (Fig. 1E). Overall, the transmission scan provides all necessary information to calculate the exact position and 3-D orientation of the stimulating coil during a PET study. This information can be used in a variety of ways, including coregistration with the (emission) PET volumes, structural MRI images, and modelled 3-D distribution of the induced electric field.

CONCLUSIONS

Transcranial magnetic stimulation is a powerful tool for manipulating neuronal activity in the human cerebral cortex. Combined with PET, it offers a unique approach to studying in vivo cortical connectivity and excitability. Interpretation of the results obtained with TMS/PET depends critically on the accuracy of positioning the coil over the target site. This can be achieved by referencing the coil position and its 3-D orientation to the MR image of the subject's cortical surface and reaching the desired position with the aid of frameless stereotaxy. The end result of coil positioning can be verified on a transmission scan, which contains a 3-D image of the TMS coil. The transmission image of the coil can also be used to merge coil-derived data, such as the modelled electric field, with emission scans and an MR image of the subject's brain.

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