TECHNIQUES AND METHODS

The Transcranial Magnetic Stimulation Motor Threshold Depends on the Distance from Coil to Underlying Cortex: A Replication in Healthy Adults Comparing Two Methods of Assessing the Distance to Cortex

Kathleen A. McConnell, Ziad Nahas, Ananda Shastri, Jeffrey P. Lorberbaum, F. Andrew Kozel, Daryl E. Bohning, and Mark S. George

Using transcranial magnetic stimulation (TMS), a hand-held electrified copper coil against the scalp produces a powerful and rapidly oscillating magnetic field, which in turn induces electrical currents in the brain. The amount of electrical energy needed for TMS to induce motor movement (called the motor threshold [MT]), varies widely across individuals. The intensity of TMS is dosed relative to the MT. Kozel et al observed in a depressed cohort that MT increases as a function of distance from coil to cortex. This article examines this relationship in a healthy cohort and compares the two methods of assessing distance to cortex.

Seventeen healthy adults had their TMS MT determined and marked with a fiducial. Magnetic resonance images showed the fiducials marking motor cortex, allowing researchers to measure distance from scalp to motor and prefontal cortex using two methods: 1) measuring a line from scalp to the nearest cortex and 2) sampling the distance from scalp to cortex of two 18-mm-square areas.

Confirming Kozel's previous finding, we observe that motor threshold increases as distance to motor cortex increased for both methods of measuring distance and that no significant correlation exists between MT and prefontal cortex distance.

Distance from TMS coil to motor cortex is an important determinant of MT in healthy and depressed adults. Distance to prefontal cortex is not correlated with MT, raising questions about the common practice of dosing prefontal stimulation using MT determined over motor cortex. Biol Psychiatry 2001;49:454–459 © 2001 Society of Biological Psychiatry

Introduction

Transcranial magnetic stimulation (TMS) is a powerful tool for brain research (George et al 1999; Ziemann et al, 2000). With TMS, an electromagnetic coil placed against a subject's scalp sends a focal and rapidly changing magnetic pulse through the skull with only minimal discomfort to the subject. Upon reaching the cortex, the magnetic field induces an electrical current that depolarizes cortical neurons. Because the magnetic field declines exponentially with distance from the coil, any condition that would increase the distance between the scalp and the surface of the subject's cortex theoretically might affect the intensity of magnetic stimulation (and thus induced electrical current) actually reaching the cortex.

Over the motor cortex, TMS causes movement in the contralateral limb or body, a visible effect. The motor threshold (MT) is defined as the lowest level of stimulation capable of causing a twitch in the contralateral thumb, specifically, the abductor pollicis brevis (APB; Pascual-Leone et al 1992). The MT varies widely across individuals but is relatively stable within individuals over time (Ziemann et al, 2000). Because of the wide range of absolute TMS intensity needed to produce comparable stimulation across individuals, most TMS researchers have attempted to correct for this variability by dosing TMS intensity as a proportion of each individual's motor threshold.

Recently, Kozel et al (2000) examined the relationship between MT, age, and the distance from the scalp to both the motor cortex and the prefrontal cortex. In their cohort of 29 depressed subjects, MT strongly correlated with distance from scalp to motor cortex ($p < .01$). Interest-

ingly, there was no significant correlation between MT and distance from scalp to prefrontal cortex, the site for repetitive TMS (rTMS) treatment of depression in their study. Kozel et al did not have a direct marker of the location of the motor cortex, however, and were forced to rely on an algorithm that derived the location of the motor cortex in relation to their more generally determined location of prefrontal cortex.

We questioned whether this relationship between MT and motor cortex distance was unique to depression and sought to test for this relationship in a group of healthy subjects stretching across a similarly broad range of ages. We also wondered whether a method of assessing distance from scalp to cortex that would sample the distance over a broad area of cortex (18 mm × 18 mm) rather than along a line (8 mm, as in Kozel's study) would produce a more accurate assessment of this distance.

Methods and Materials

Subjects

Seventeen healthy adults (9 men) between the ages of 19 and 75 (mean = 43, SD = 20) participated. Subjects were screened for health problems using a detailed history-taking and physical examination. Additionally, subjects over age 60 completed and passed mini-mental status exams to screen for dementia (Folstein et al 1975; mean score = 30, SD = 1, cutoff = 26). All subjects gave written informed consent as approved by the Medical University of South Carolina internal review board.

Transcranial Magnetic Stimulation and Magnetic Resonance Method

As previously described in Bohning et al (1999), subjects had their MT and optimal spot for APB movement determined using visible twitch and the method of limits while outside the scanner (Pridmore et al 1998). The TMS coil, including fiducials attached at the center and on either end, was then mounted on a holding device designed specifically for combining TMS with magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) and described fully by Bohning et al (1999). Subjects were placed on the MRI bed with their head inside the MRI radio frequency (RF) head coil and against the TMS coil. With subjects in this position, researchers stimulated each subject making minor adjustments in head placement to find again the MT and stimulation site for APB. Each subject's head was then stabilized in this position with inflatable cushions. Both stimulation site and MT were then verified before the subject and TMS coil were advanced together inside the scanner. Once inside the scanner and after the initial scanner tuning and shimming, placement and MT were verified for the third and final time before acquiring the structural images of interest (twelve 5-mm slices, 1.5-mm gaps centered over motor cortex). The configuration for combining TMS and MRI and more detailed acquisition parameters have been described previously (Bohning et al 1999; Shastri et al 1999).

Data Analysis

We converted the scans to ANALYZE AVW format and transferred them to SUN Workstations. The images were analyzed twice, once using MEDx 3.0 software in a manner that followed Kozel's method (Replication Method) and a second time using Analyze software sampling the distance over a square area of cortex (Method of Sampling a Square).

Method of Determining the Location of Motor and Prefrontal Cortex

As described above, we located and marked the motor cortex area for APB with the center fiducial on our TMS coil. Considering that our slices are 5 mm thick with 1.5-mm gaps, measuring on two coronal slices samples a region of cortex 11.5 mm in length, anterior to posterior, which corresponds to the anterior–posterior length of Brodman's area 4, Gyrus precentralis, as reported in the Talaraich atlas (Talaraich and Tournoux 1998) at the approximate axial level of stimulation of APB (y, −04 mm to −17; z, +45). Brodman's area 8, Gyrus frontalis medialis, begins about 18 mm, or three slices, anterior to this site and extends at least 20 mm, or another three slices, anteriorly from there.

Replication Method of Measuring Distance

Replicating Kozel's standardized method (interrater reliability with Kozel's 95%), a trained rater (KM) using a semiautomated graphics feature of MEDx 3.0 (Sensor Systems; Sterling, VA), measured the distance on a coronal MRI from the outside edge of the scalp just under the fiducial to the nearest cortical surface on two groups of contiguous slices, one group each for prefrontal and motor cortex, and averaged the results. Variation in acquisition parameters necessitated the following adjustments. For each subject, rather than measuring and averaging the distances over eight contiguous 1-mm slices, the rater collected two measurements on two consecutive slices, the slice with the brightest image of the center fiducial and the one anterior to it. She then averaged these measurements to produce one distance measurement for each subject that represented the average distance from scalp to motor cortex over an 11.5-mm-wide strip of motor cortex.

Using the same method described above, the rater measured three consecutive slices over the prefrontal cortex which was defined as the area 18 mm, or three slices anterior to the site representing motor cortex.

Method of Sampling a Square

Using the "sample region of interest" feature of ANALYZE, the same rater (KM) demarcated three regions of interest: outlining the surface of the head, outlining the surface of the brain, and an 18-mm-wide rectangle long enough to cover the distance from the scalp to the surface of the brain oriented at a 30-degree angle and centered over the fiducial marking motor cortex as above. We chose to angle our region of interest at 30 degrees because that was the approximate angle of the TMS coil in those coronal images where all three fiducials (center and either end) were
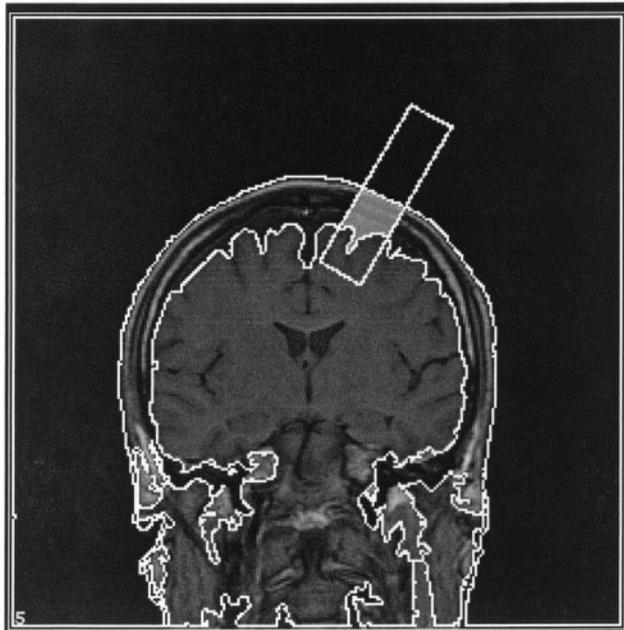
Figure 1. Magnetic resonance image in ANALYZE imaging software demonstrating a method of measuring the distance from scalp to cortex at the site of TMS stimulation by drawing a consistent rectangle, outlining the surface of cortex and scalp, and sampling the intervening area in mm^2.

visible in one slice. The rater sampled the area in square millimeters of the region of the rectangle between the scalp and the surface of the cortex as illustrated in Figure 1. She acquired and averaged these measurements for the same slices as those described in the replication method.

Statistical analyses were performed using STATView 4.5 software.

Results

Replication Method

DISTANCE AND MT. Confirming the prestudy hypothesis and replicating the prior Kozel study in this healthy cohort, MT significantly increased with increasing distance between scalp and motor cortex (Figure 2) (Fisher R to Z, hypothesized correlation < 0, $p = .0006$, $R^2 = .491$, slope $= 5.261$).

We found that MT did not significantly correlate with distance from scalp to prefrontal cortex (Fisher R to Z, hypothesized correlation < 0, $p = .0973$, $R^2 = .111$, slope $= 1.923$).

MOTOR CORTEX DISTANCE AND PREFRONTAL CORTEX DISTANCE. The distance from scalp to motor cortex significantly correlated with distance from scalp to prefrontal cortex (Figures 3 and 4) (Fisher R to Z, hypothe-
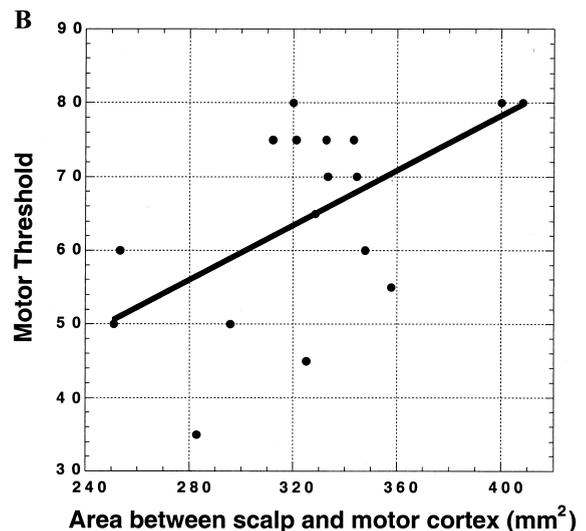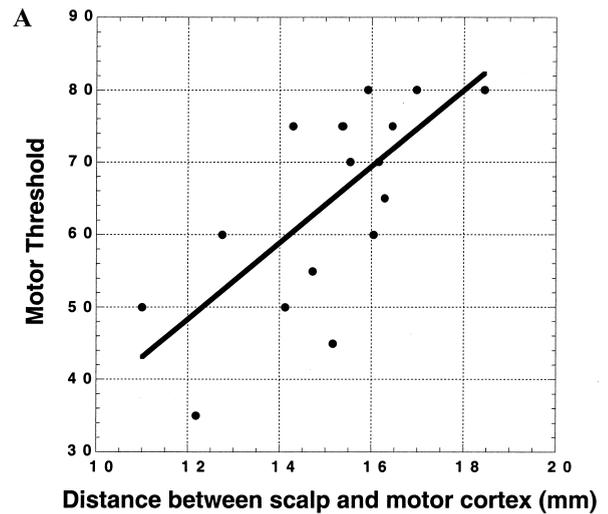

Figure 2. Graphs illustrating the correlation between distance from scalp to motor cortex and motor threshold using (**A**) Kozel's method of measuring distance from scalp to cortex along a line and (**B**) a method of measuring distance from scalp to cortex using the area of a rectangle drawn over the cortex as illustrated in Figure 1. The motor threshold is expressed as a percent of the maximum machine output for the modified Dantec TMS coil in the magnetic resonance imaging scanner using a figure-eight coil.

sized correlation < 0, $p = .0057$, $R^2 = .347$, slope $= 0.767$).

CORRELATION WITH AGE. There was no significant correlation between age and increased distance from scalp to motor cortex (Fisher R to Z, hypothesized correlation < 0, $p = .0732$, $R^2 = .137$, slope $= 0.034$), and there was no
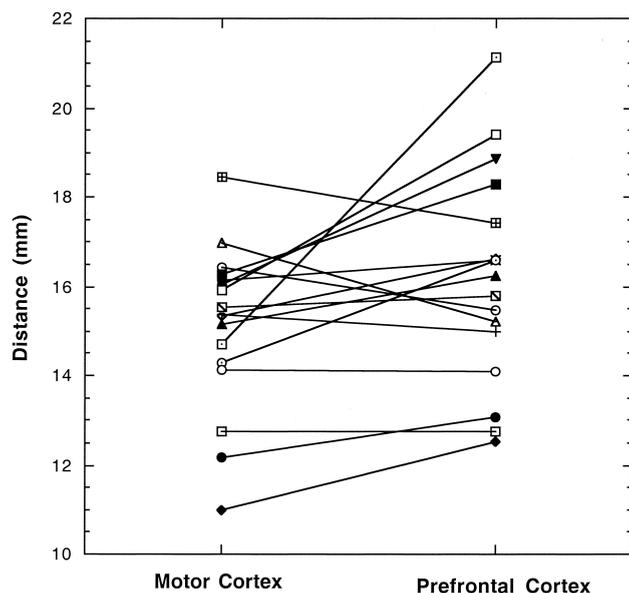
Figure 3. This scatter plot displays the relationship between distance over motor cortex and distance over prefrontal cortex for each subject. Note that although prefrontal distance tends to be greater than motor distance, this relationship is not universal for all subjects; in some individuals, the motor distance is greater than prefrontal distance. This large variation suggests that dosing prefrontal stimulation on intensities determined over motor cortex may be problematic.
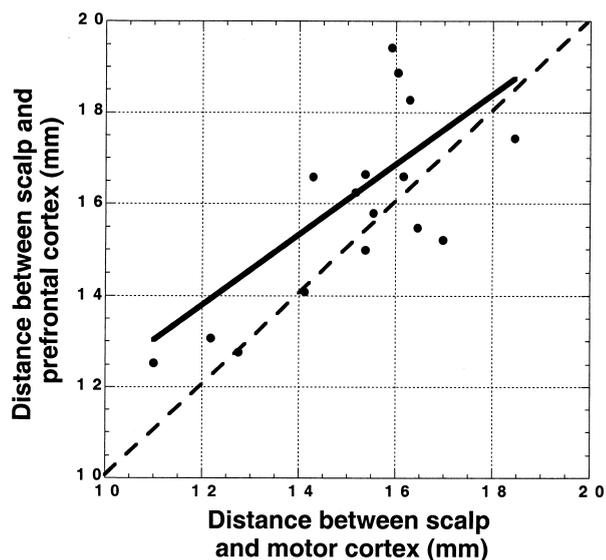

Figure 4. A two-way scatter plot illustrating the relationship between motor cortex distance and prefrontal cortex distance. These two distances correlated using both methods of anatomic measurement (solid line). The broken line shows that although for most subjects the prefrontal distance was greater, in four subjects the two distances were almost the same, and in five subjects the prefrontal distance was less than the motor cortex distance.

significant correlation between age and distance from scalp to prefrontal cortex (Fisher R to Z, hypothesized correlation < 0, $p = .2974$, $R^2 = .02$, slope $= 0.017$). There was also no significant correlation between age and MT (Fisher R to Z, hypothesized correlation < 0, $p = .1397$, $R^2 = .079$, slope $= 0.195$).

Method of Sampling a Square

DISTANCE AND MT. We found that MT significantly increased with increasing distance between scalp and motor cortex (Figure 2B) (Fisher R to Z, hypothesized correlation < 0, $p = .0079$, $R^2 = .323$, slope $= 0.185$).

We also found that MT did not correlate with increasing distance between scalp and prefrontal cortex (Fisher R to Z, hypothesized correlation < 0, $p = .0894$, $R^2 = .119$, slope $= 0.094$).

MOTOR CORTEX DISTANCE AND PREFRONTAL COR-TEX DISTANCE. The distance from scalp to motor cortex correlated with the distance from scalp to prefrontal cortex (Fisher R to Z, hypothesized correlation < 0, $p = .0084$, $R^2 = .318$, slope $= 0.674$).

CORRELATION WITH AGE. There was a significant correlation between age and increased distance from scalp to motor cortex (Fisher R to Z, hypothesized correlation $<$

0, $p = .0120$, $R^2 = .291$, slope $= 1.144$), but not between age and distance from scalp to prefrontal cortex (Fisher R to Z, hypothesized correlation < 0, $p = .1521$, $R^2 = .072$, slope $= 0.679$). There was no correlation between MT and age (Fisher R to Z, hypothesized correlation < 0, $p = .1397$, $R^2 = .079$, slope $= 0.195$).

Discussion

Our findings in this healthy and medication-free cohort are an important replication of Kozel's work with depressed patients because we demonstrate that the relationship between motor threshold and distance from scalp to cortex is a feature of normal anatomy and physiology, not a pathologic consequence of depression.

This study also compares two methods of assessing distance from scalp to cortex using the same data. Both methods confirm the results from Kozel's study that as distance increased in motor cortex, MT also increased, and that this tight relationship does not hold for MT and the distance over prefrontal cortex. This study also demonstrates that, although motor distance significantly correlated with prefrontal distance and prefrontal distance tended to be greater than motor cortex distance for most subjects, the prefrontal distance was not longer for all subjects (replication method, 5 out of 17 subjects' motor cortex was greater than prefontal cortex distance; method

of measuring a square, 8 out of 17 subjects' motor cortex distance was greater than prefontal cortex distance). These results raise questions concerning the current method for dosing TMS to all "silent" areas of the brain that relies on the level of TMS stimulation an individual requires relative to their MT. They further suggest that dosing TMS should take into account the distance from scalp to cortex over the specific area to be stimulated, not just over motor cortex. In a previous paper, Bohning et al proposed a formula for calculating the exponential drop in field strength as one moves further from the TMS coil (Bohning et al 2000). For future studies of TMS over nonmotor areas and ignoring for the moment the logistic complications of routine MRI scanning for all TMS subjects, it should be fairly simple to measure the distance from scalp to cortex in a subject's structural MRI and use the above formula to calculate an even more accurate dosage for TMS than even the current gold standard of dosing as a percentage of MT. In an open study at the Medical University of South Carolina of TMS treatment of depression in a geriatric population, this technique is already showing promise.

The two methods of assessing distance presented in this article diverged on only one point. The method of measuring an area of cortex rather than a line demonstrated a significant correlation between age and distance over motor cortex ($p = .01$), whereas Kozel's method of measuring a line did not ($p = .07$). Given that generalized cortical atrophy is a well-documented feature of normal aging, these data alone would suggest that the new method of measuring a square is more accurate. Our reasoning in developing this second method was that given the irregular topography of the brain's surface caused by cortical folding, a focal method of measuring distance would be more susceptible to variation than would a method that samples a broader region of the brain's surface. Furthermore, we sought to compare the relationship between motor and prefrontal cortex distance and MT. Although the motor cortex is a region of brain that is very focally dedicated to its functions and precisely mapped, current knowledge of prefrontal cortex is comparatively diffuse, both in form and function. So although motor cortex predictably corresponds to the precentral gyrus, prefrontal cortex extends over several gyri and sulci. Thus, this method of sampling distance from scalp to cortex over an area of cortex rather than along a line might also more fairly accommodate the topographic variability between the two sites within individuals and thus more accurately assess their relationship to MT. Furthermore, Kozel's method of measuring the nearest cortex selects the shortest distance from scalp to cortex without regard to the angle at which this line is drawn. In practice, this method produces considerable variation in the angle of measurement and

arbitrarily selects the shortest distance in the vicinity of the target site. Because age-related atrophy appears morphologically as an expansion of sulci more than simple shortening of gyri, Kozel's method is insensitive to the topographic changes caused by normal age-related atrophy, which probably accounts for this method's failure to observe the well-established relationship between advanced age and increased distance from scalp to cortex.

Our study is limited by its small sample size ($n = 17$); however, the subjects were rigorously screened and represented a broad age range (19–75).

We acquired this data in a spatially crude manner (5 mm/skip 1.5 mm) relative to Kozel's method, which acquired 1-mm slices. Nonetheless, given that age-related atrophy and related conditions that tend to manifest as increased distance from scalp to cortex are regional and not focal phenomena, as well as the above argument for the greater accuracy of a regional over a focal method of assessing distance, these relatively thick slices and wide interslice gaps actually enhance rather than limit the accuracy of our measurements.

References

Bohning DE (2000): Introduction and overview of TMS physics. In: *Transcranial Magnetic Stimulation in Neuropsychiatry.* Washington, DC: American Psychiatric Press.

Bohning DE, Shastri A, McConnell KA, Nahas Z, Lorberbaum J, Roberts D, et al (1999): A combined TMS/fMRIstudy of intensity-dependent TMS over motor cortex. *Biol Psychiatry* 45:385–394.

Folstein MF, Folstein SE, McHugh PR (1975): Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198.

George MS, Lisanby SH, Sackeim HA (1999): Transcranial magnetic stimulation: Applications in neuropsychiatry. *Arch Gen Psychiatry* 56:300–311.

Kozel FA, Nahas Z, deBrux C, Molloy M, Lorberbaum JP, Bohning D, et al (2000): How coil-cortex distance relates to age, motor threshold, and possibly the antidepressant response to repetitive transcranial magnetic stimulation (rTMS). *J Neuropsychiatry Clin Neurosci* 12:376–384.

Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, Cohen LG, Hallett M (1992): Seizure induction and transcranial magnetic stimulation. *Lancet* 339:997.

Pridmore S, Filho JAF, Nahas Z, Liberatos C, George MS (1998): Motor threshold in transcranial magnetic stimulation:

A comparison of a neurophysiological and a visualization of movement method. *J ECT* 14:25–27.

Shastri A, George MS, Bohning DE (1999): Performance of a system for interleaving transcranial magnetic stimulation with steady state magnetic resonance imaging. *Electroencephalogr Clin Electrophysiol* 51:55–64.

Talaraich J, Tournoux P (1988): *Co-Planar Stereotactic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging.* New York: Thieme.

Ziemann U, Hallett M (2000): Basic neurophysiological studies with TMS. In: *Transcranial Magnetic Stimulation in Neuropsychiatry.* Washington, DC: American Psychiatric Press.