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Static field influences on transcranial magnetic stimulation: Considerations for TMS in the scanner environment

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Abstract

Background: Transcranial magnetic stimulation (TMS) can be combined with functional magnetic resonance imaging (fMRI) to simultaneously manipulate and monitor human cortical responses. Although tremendous efforts have been directed at characterizing the impact of TMS on image acquisition, the influence of the scanner's static field on the TMS coil has received limited attention.

Objective/Hypothesis: The aim of this study was to characterize the influence of the scanner's static field on TMS. We hypothesized that spatial variations in the static field could account for TMS field variations in the scanner environment.

Methods: Using a MRI-compatible TMS coil, we estimated TMS field strengths based on TMS-induced voltage changes measured in a search coil. We compared peak field strengths obtained with the TMS coil positioned at different locations (B_0 field vs fringe field) and orientations in the static field. We also measured the scanner's static field to derive a field map to account for TMS field variations.

Results: TMS field strength scaled depending on coil location and orientation with respect to the static field. Larger TMS field variations were observed in fringe field regions near the gantry as compared to regions inside the bore or further removed from the bore. The scanner's static field also exhibited the greatest spatial variations in fringe field regions near the gantry.

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Conclusions: The scanner's static field influences TMS fields and spatial variations in the static field correlate with TMS field variations. TMS field variations can be minimized by delivering TMS in the bore or outside of the 0 - 70 cm region from the bore entrance.

Introduction

Transcranial magnetic stimulation (TMS) can be used within the MRI scanner to noninvasively manipulate brain activity while subjects undergo functional neuroimaging. As the technical challenges related to delivering TMS in the scanner have been overcome (1-7), this multimodal approach has been increasingly used to causally map motor, sensory, and cognitive brain networks in humans (8-10). Importantly, while great attention and effort has been directed to accounting and correcting for TMS influences on image acquisition (1-4), the influence of the scanner's magnetic field on TMS remains relatively unexplored.

TMS can be shaped by nearby magnetic fields (11, 12), so the scanner's static field likely influences the TMS coil's field. Spatial distortions of the TMS field could result in increased variability in TMS-evoked responses and challenge data quality. More critically, variability in TMS fields can lead to variations in the effective intensity of stimulation and these changes could pose significant risks to TMS recipients. Indeed, the determination of stimulation intensity is a crucial aspect in the design of TMS studies (13, 14). For these reasons, accounting for static field influences on TMS may be especially important for concurrent (or interleaved) TMS-fMRI experiments where TMS is delivered in the scanner bore. Moreover, repetitive TMS (rTMS) paradigms are now combined serially with functional neuroimaging in efforts to visualize the hemodynamic consequences of targeted neuromodulation (15-18). To minimize the time between the neuromodulation interventions and the onset of scanning, rTMS is sometimes delivered in the fringe field immediately outside the bore (19, 20). For these experiments, a better understanding of static field influences on TMS is clearly necessary to ensure the safety of participants.

Here we characterized static field influences on TMS using a search coil designed to measure TMS-induced electrical fields. We measured TMS fields while manipulating the TMS coil's location and orientation within the scanner environment, specifically testing responses in static field regions where TMS is likely to be delivered during the staging and execution of TMS experiments, namely in the bore and in the fringe field near the gantry. We hypothesized that at different locations in the scanner environment, spatial variations of the static field would exert varying influences on the TMS coil, resulting in variability in TMS fields across coil arrangements. We calculated spatial variations in the static field and related these to TMS field measurements.

Materials and Methods

Measuring TMS field strength in the scanner environment

Bi-phasic magnetic pulses were delivered using a Magstim Rapid² unit (Magstim Co., Dyfed, UK) and a MRI-compatible figure-of-eight coil (70mm wing diameter). A custom filter box (Magstim Co.) connected the TMS coil to the stimulator unit. Coil tests were conducted at the F. M. Kirby Research Center for Functional Brain Imaging at the Kennedy

Krieger Institute and we characterized the influence of the static field of a Philips Intera 3.0 Tesla (3T) scanner (Philips Healthcare, Best, The Netherlands). The TMS coil was secured to the scanner bed using a custom-built plastic holder that enabled precise and stable coil positioning. All tests performed in the scanner environment were conducted in the absence of image acquisition. For a baseline condition establishing TMS field strength outside of the static field, we measured TMS fields with the MRI-compatible coil located in the hallway adjacent to the scanner room. The same setup (i.e., coil, stimulation unit, filter, and connecting cables) was used for baseline measurements and measurements taken in the scanner environment.

We quantified TMS field strength by measuring induced voltage changes in a six-turn search coil (Figure 1A, *left*) with an average loop area of 2500 mm^2 (for a total loop area of 0.015 m^2). On separate days, for each experiment, the search coil was temporarily mounted to the TMS coil using a plastic supporting frame (Figure 1A, *right*). Insulated wires from the search coil were twisted to prevent the time-varying magnetic field from inducing voltage changes in the leads. These wires connected to a digital oscilloscope (Tektronix TDS 3014B). Voltage traces (Figure 1B) on the oscilloscope were saved and transferred to a PC for offline analysis. As seen in Figure 1B, the voltage traces contained slight oscillations which resulted from the search coil's internal resonance from its inherent capacitance and inductance when the Magstim Rapid switches turned on and off. Because these oscillations are very fast and their total area is zero, they could be removed via integration, which serves to mathematically filter the high frequency content of the voltage trace and to isolate the slower component corresponding to the magnetic field. Accordingly, for each trial we integrated the voltage measurements (baseline-subtracted voltage time series) to derive the peak magnetic field. In each experiment, we compared peak flux at each coil arrangement, averaged over 10 repetitions. Because the precise seating of the search coil against the TMS coil differed slightly in each experiment, field measurements from experiments conducted on separate sessions across days could not be directly compared. All data processing and analysis were performed using Matlab.

In Experiment 1, we tested the general hypothesis that TMS fields in the scanner environment are influenced by the static field. In this test, we used a $2 \times 2 \times 2$ factorial design that assessed how manipulations of coil location, coil orientation, and stimulation intensity impacted TMS field strength. The coil was located either outside the scanner (in the fringe field) or within the scanner (in the homogeneous B_0 field). For measurements in the fringe field, the coil was mounted to the bed near the gantry where a participant would typically lay his head during the staging of neuroimaging scans: This location fell approximately 60cm outside of the gantry, as measured from the scanner's external alignment lasers. For measurements in the B_0 field, the bed was retracted into the gantry until the TMS coil fell within the center of the bore (approximately 75cm from the alignment lasers), as done in typical neuroimaging scans. (The static field at this location is strongly homogeneous to support longitudinal magnetization in MR imaging). Coil orientation was either horizontal or vertical, with respect to the horizontal plane of the scanner bed. For each coil manipulation, we made field measurements with TMS intensity set at 50% or 90% stimulator output (10 observations each).

In Experiment 2, we focused exclusively on measurements in the fringe field near the gantry to more comprehensively sample the range of coil orientation manipulations in the static field area exhibiting the largest TMS field variations. In addition to characterizing TMS fields according to coil orientation (i.e., vertical versus horizontal), we measured TMS fields as the coil was rotated about the z-axis (i.e., orthogonal to the scanner bed surface). Stimulation intensity was fixed at 90% stimulator output.

To develop a preliminary model relating static field measurements to TMS field variations in the scanner environment, we mapped the static field by taking point-measurements of magnetic field strength across a grid of positions (4×13) spanning the inside of the bore and the fringe field. Measurements were recorded at 13 distances in the Head–Foot (y-) axis, relative to the alignment laser in the gantry: -120, -100, -80, -60, -40, -20, 0, 20, 40, 60, 80, 140, 200 cm (negative values indicate locations inside the scanner). At each distance, measurements were recorded at 4 positions in the Left–Right (x-) axis, each separated by 2in, spanning the middle of the scanner bed: These positions were selected to cover the space most likely to be occupied by the TMS coil during experiments. At each grid location, we assessed the strength of the static field with a 1-axis Gaussmeter (AlphaLab, Inc; Model GM2). Because the device measured field strength in a single axis, we probed for field strength (using the peak hold function) at each grid position with the sensor fixed at different rotations about the z-axis (in 45° steps). Thus, at each grid position, we had 8 field values that enabled us to approximate the peak magnitude and direction of the static field (of course, the absolute magnitudes of measurement pairs with the probe rotated 180° relative to each other were highly similar). These measurements only capture field map variations in a single horizontal plane (4in above the scanner bed) and ignore field strength in other planes (oblique to vertical) and other elevations.

Results

In the scanner environment, we reliably measured voltage induction by bi-phasic TMS pulses in a six-turn search coil (Figure 1B, black trace) and magnetic field estimates were robust and consistent (Figure 1B, gray trace). The shape and time course of these recordings are consistent with previous characterizations of Magstim Rapid responses (21). As expected, low-intensity TMS induced significantly weaker magnetic fields compared to high-intensity TMS (intensity main effect, $p < 10^{-10}$). At low TMS intensities (Figure 2B), field measurements were significantly modulated by coil manipulations ($p < 10^{-10}$): The strongest TMS fields were observed with the coil outside of the scanner environment. Within the scanner environment, TMS coil measurements depended significantly on coil location ($p < 10^{-10}$) and coil orientation ($p < 0.005$) and there was a significant location $\times$ orientation interaction ($p < 10^{-10}$). Importantly, TMS strength did not differ between horizontal and vertical orientation manipulations within the B_0 field ($t(18) = 1.9$, $p = 0.08$). In contrast, whether the coil was oriented horizontally or vertically in the fringe field significantly impacted TMS field strength ($t(18) = 20.1$, $p < 10^{-10}$): The average field measured at the horizontal orientation was 94.8% that of fields measured at the vertical orientation. With high intensity TMS (Figure 2C) we observed a similar pattern of modulation effects ($p < 10^{-10}$). Coil orientation significantly determined TMS strength in the fringe field ($t(18) = 16.1$, $p < 10^{-10}$), but not in the B_0 field ($t(18) = 1.3$, $p = 0.21$).

Notably, as with low-intensity TMS, TMS fields were weaker at horizontal compared to vertical orientations, but the difference between orientations was smaller with high-intensity TMS (Horizontal/Vertical ratio: 96.3%). This suggests that the influence of the static field scales inversely with TMS intensity.

In the fringe field, TMS field measurements differed depending on whether the coil was oriented vertically or horizontally, but these manipulations ignored rotation about the z-axis, the axis perpendicular to the scanner bed. Rotation in this dimension may be critical because this manipulation changes the coverage of the coil in the horizontal plane and static field flux lines change dramatically along the horizontal plane extending away from the scanner, especially in the region near the gantry where the coil was fixed (see below). Because the degree to which segments of the TMS coil were exposed to fields differing in strength likely covaried with orientation changes in Experiment 1, coil orientation, per se, may not have been the critical determinant of TMS field variations. We tested this possibility in Experiment 2 by measuring coil responses in the fringe field (at vertical and horizontal orientations) while manipulating the coil's rotation about the z-axis (Figure 3A). In these measurements, stimulation intensity was set at 90% stimulator output. Coil manipulations (Figure 3A) significantly modulated TMS fields ($p < 10^{-10}$). Vertical condition i, matching the vertical condition in Experiment 1, yielded the largest fields that were significantly greater than measurements at both horizontal orientations (iv and v; all $p < 10^{-6}$). These patterns, specifically the comparison between conditions i and v, replicate the results in Experiment 1. Critically, the TMS field was also weaker when the coil was vertical but rotated (conditions ii and iii; all $p < 10^{-9}$). Because coil orientation is constant across conditions i, ii, and iii, scanner interactions with the TMS coil cannot be determined explicitly by the coil's orientation. Instead, considering that the TMS coil spans the x-, y-, and z-axis disproportionately across test conditions, these results imply that static field variations in the space occupied by the coil determines the scanner's influence on TMS fields.

To directly relate spatial variation in the static field to the observed TMS effects, we estimated the scanner's static field map by probing magnetic field strength (in the absence of TMS) across a grid of positions spanning the fringe field and the B_0 field (Materials and Methods). Although we were mainly interested in field magnitudes at each position, we confirmed that the primary direction of the flux lines were along the Head-to-Foot direction (i.e., moving away from the bore) using peak field measurements recorded at 8 orientations (rotated about the z-axis) at each grid position. Additionally, we confirmed that flux lines bent gradually away from the midline of the scanner bed: Moving away from the bore, measurements recorded at positions to the right of midline exhibited slightly greater fields directed rightward and measurements to the left of midline exhibited a comparable leftward bias.

In assessing field magnitude, we found that peak field strength varied little over measurements taken along the Left–Right axis (i.e., x-axis) at fixed distances from the gantry. For instance, peak static field measurements recorded 60cm away from the gantry, where we observed the largest variations in TMS fields, ranged from 2218.5–2263.6 G – this corresponded to a maximum difference of 45.1 G or 0.0045 T over 4 positions spanning 8

inches the x-axis. In contrast, substantially larger static field variations were observed in the Head–Foot axis (i.e., y-axis). Figure 4A displays the average peak strength of the static field measured at 13 distances relative to the gantry (Materials and Methods) and we estimated peak field values between the measured points using cubic interpolation. Field strength hovered near 3 T in scanner bore and decayed rapidly and nonlinearly as a function of distance away from the gantry (Figure 4A).

To relate static field variations in the y-axis to TMS field variations, we first calculated the range of static field variations that a TMS coil maximally spanning the y-axis would encounter. To do so, we considered the maximum (wingtip-to-wingtip) length of the TMS coil to be 14cm (given the 70mm diameter loops comprising each wing). We then estimated the spatial variation in the static field that a coil positioned anywhere along the y-axis would encounter by computing the sliding difference in peak static field between 2 points separated by 14cm along the y-axis (Figure 4B). This trace indicated that static field variations, over any 14cm segment, were large in fringe field regions near the gantry and minimal in the B_0 field and in fringe field regions more distal from the gantry. To directly relate the static field variations to TMS field variations (Figure 4B, inset plot), we determined the static field differences estimated for the test locations in Experiments 1 and 2, namely the B_0 field (circle marker) and the fringe field near the gantry (square marker). Additionally, we tested TMS field variations in a fringe field region further removed from the bore, approximately 100 cm from the gantry (diamond marker). (For these measurements, the setup used to compare horizontally versus vertically oriented coils in Experiments 1 was repeated, with stimulator intensity set at 50% output). Including measurements acquired with high-intensity TMS (filled markers) and low-intensity TMS (open markers), we computed the correlation between TMS field variations (summarized by the field strength ratio between horizontally and vertically oriented coils where a value near 1 indicates more similar TMS field strengths across orientations) and static field variations. We found a significant relationship ($r = -0.87$, $p = 0.01$) indicating that smaller static field variations corresponded to smaller TMS field variations (Figure 4B, inset plot). While this relationship held for both high-intensity TMS and low-intensity TMS, high-intensity TMS generally appeared to be less susceptible to the influence of the static field (filled vs open markers).

Discussion

Here we show that the scanner's static field can exert robust and systematic influences on TMS-induced electrical field measurements. TMS fields were generally smaller in the scanner environment and field strength varied depending on coil location and orientation. We found that coil orientation changes in the B_0 field did not result in substantial TMS field variations. In contrast, TMS fields measured immediately outside the gantry were much more sensitive to coil manipulations. Additionally, by varying TMS intensity we found that TMS field variations in the fringe field were smaller at higher TMS intensity – In other words, the static field less influenced stronger TMS pulses compared to weaker pulses. Lastly, we mapped the scanner's static field and concluded that spatial variations in the static field, most prominent in the fringe field outside the gantry and larger in the Head–Foot axis, accounted for TMS field variations.

Our primary observation – that TMS field variations within the homogeneous B_0 field are minimal – is important validation for the practice of delivering TMS in the scanner during functional neuroimaging. In fact, concurrent (or interleaved) TMS-fMRI is an increasingly popular multimodal research tool used for studying brain connectivity (9, 10), made more popular with recent technical advances and increased accessibility to MRI-compatible technologies. Our results contribute to a growing body of literature providing assurances for the general feasibility and reliability of TMS use within the MRI scanner. Moreover, our results also suggest that it is appropriate to target different cortical areas in the same fMRI experiment, even if coil orientation changes dramatically between target sites. This recommendation may be useful while considering control conditions and analysis contrasts when designing concurrent TMS-fMRI experiments.

In contrast to the small effects observed in the B_0 field, TMS field measurements were more variable when the coil was positioned in the fringe field immediately outside the gantry where we observed TMS field variations that exceeded 5% of the maximum field strength. Understanding TMS behavior in the fringe field is worthwhile because the fringe field is used routinely as a staging area for equipment positioning and calibration in concurrent TMS-fMRI studies (16, 22). (The fringe field is often used as a staging area for any fMRI scan involving specialized hardware). Staging is especially critical for concurrent TMS-fMRI experiments because the radiofrequency coil and the bore itself limit direct access to the space around the participant's head and prohibit fine adjustments of the TMS coil when the participant is retracted into the scanner – therefore, coil positioning and intensity calibration need to be optimized in the fringe field. Moreover, fringe field effects are important considerations for researchers combining brain stimulation and fMRI serially (rather than concurrently) with the goal of visualizing the hemodynamic consequences of neuromodulation interventions. While this practice often involves rTMS delivery outside of the scanner room (15, 17, 18), rTMS has also been delivered in the fringe field (19, 20) or within the scanner (16) to minimize the time between neuromodulation and scanning. For such TMS applications, our results reaffirm that calibrated TMS intensities (e.g., motor thresholds) established outside of the scanner environment should not be applied to the scanner room (22). Furthermore, calibrated intensities established in the static field at one coil arrangement cannot be assumed to generalize to other coil arrangements.

The importance of TMS intensity calibration, or dosing, has been thoroughly discussed elsewhere (13), but some basic considerations are worth reiterating here. First, dosing is recommended because responsiveness to TMS can vary greatly across the general population, which makes stimulation intensity settings that account for TMS efficacy in individuals preferable over fixed and arbitrary intensity settings based stimulator output (14). Indeed, well-established safety guidelines for TMS use stipulate clear intensity settings that are based on normalized response thresholds (typically, the motor threshold) defined for individual participants (13, 14) and these recommendations are crucial for rTMS interventions where stimulation at higher intensities can induce seizure activity. In this regard, consideration of fringe field TMS effects is important for participant safety as 5% changes in TMS intensity, particularly at levels near motor threshold, can result in substantial increases in evoked response magnitude (22, 23). Furthermore, the steepness of the input-output (recruitment) curve scales as a function of tonic activation level (23), so the

actual impact of the fringe field on TMS responses may be further exacerbated if the participant is actively engaging the targeted brain region. Thus, considerations of dosing and the potential impact of the static field on calibrated intensities are especially critical for TMS applications in the scanner environment. However, despite inter-individual variability in TMS responsiveness, due to the difficulty establishing individualized intensity settings in the scanner, it may be more practical to apply a fixed, albeit reduced and definitively safe, intensity setting to all participants.

Although our results unambiguously demonstrate that the static field influences the TMS coil, we are only able to provide a preliminary descriptive model of their interaction. We hypothesized that spatial variations in the static field could account for the observed TMS effects and we reasoned that TMS field variations in the static field resulted from different portions of the coil occupying regions of space with highly disparate static field strengths. By probing the strength of the static field across the scanner environment, we found that the static field near the gantry was highly heterogeneous, exhibiting rapid field changes over very short distances, especially in the Head–Foot axis compared to the Left–Right axis. Specifically, in the fringe field near the gantry where we measured the greatest TMS variations, static field differences in the y-axis exceeded 850 G whereas static field differences over a comparable distance in the x-axis differed by a mere 45.1 G. That spatial variations in the y-axis, rather than the x-axis, were more likely to impact TMS fields is consistent with the results of Experiments 1 and 2: In the condition exhibiting the smallest influence of the static field, the TMS coil was always oriented vertically such that it minimally occupied space in the y-axis. Conversely, TMS fields were always reduced when the coil was positioned to span more extensively in the y-axis. Notably, TMS fields were also reduced when the coil occupied extensive area in the vertical z-axis (see condition iii in Experiment 2). Although we did not map static field variations across elevations, this result implies that the static field changes along this axis can be substantial. Finally, we found that static field variations in the homogeneous B_0 field and in more distal fringe field regions are greatly reduced and TMS field variations in these regions are concomitantly reduced. Together, these results 1) validate the use of TMS in the bore and 2) recommend that TMS delivery in the fringe field, if necessary, be conducted at locations further removed from the bore. Based on the inflection point in the field difference trace in Figure 4B, we recommend that TMS use in the fringe field occur at a distance greater than 70cm from the gantry.

In summary, although TMS fields in the B_0 field can be considered reliable over changes in coil position, such assurances do not extend to TMS application in the fringe field near the gantry. Many experimental factors are known to influence TMS efficacy, such as the orientation of the coil relative to the brain (21), the dynamic state of the targeted brain region (24), and participants' anxiety level (13). For concurrent TMS/fMRI experiments or other types of TMS administration in the scanner environment, we conclude that another potential source of variability in TMS responses is the coil's interaction with the static field. Fortunately, this factor can be easily controlled by restricting stimulation to regions that are either within the bore or outside of the 0 - 70 cm region from the bore entrance, thereby ensuring data quality and the safety of research participants.

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Figure 1.

A, TMS-induced voltage changes were measured in a 6-turn search coil (*left*). The diagram (*right*) depicts a profile view of the coil setup displaying the search coil mounted to the stimulating surface of a figure-of-eight TMS coil (70-mm wing diameter). The coil's magnetic field is generated in the direction indicated by the arrow. **B**, Magnetic field output of the stimulator (*black*) averaged over 10 TMS discharges. Field trace is derived from the integration of the voltage trace (*gray*) measured in the search coil (see Materials and Methods). These example traces were measured in the fringe field near the gantry with the coil oriented horizontally with respect to the scanner bed and with TMS intensity set at 50% stimulator output.

Figure 2.

A, Experiment 1 schematic depicts TMS coil's placement location (B_0 field or fringe field) and orientation (horizontal or vertical) in scanner. Each row summarizes a particular coil arrangement (labels on the left). Columns indicate different perspectives of the coil arrangements: Side view, Overhead view, and Bore-facing view (F = foot, H = head, T = top, B = bottom). **B**, Peak field measurements for low-intensity TMS (50% stimulator output). Averages are shown for measurements acquired outside of the scanner environment (No field), in the fringe field, and in the bore (B_0 field). (V = vertical, H = horizontal). Error bars indicate s.e.m. TMS field strength was significantly modulated by coil location and orientation. **E**, Peak field measurements for high-intensity TMS (90% stimulator output). Conventions as in B.

Figure 3.

A, Experiment 2 schematic depicts TMS coil's placement location (fringe field only) and orientation (horizontal or vertical) in scanner environment. This experiment explicitly tested the impact of coil rotations about the z-axis. Each row summarizes a particular coil arrangement (labels on the left): There were 3 distinct arrangements with the coil oriented vertically (i, ii, iii) and 2 with the coil oriented horizontally (iv, v). Columns indicate different perspectives of the coil arrangements: Side view, Overhead view, and Bore-facing view (F = foot, H = head, T = top, B = bottom). **B**, Peak field measurements for high-intensity TMS (90% stimulator output) at vertical (i-iii) and horizontal (iv and v) coil orientations. Error bars indicate s.e.m. TMS fields were modulated in both vertical and horizontal arrangements indicating that static field influences did not depend on coil orientation, per se.

Figure 4.

A, Static field strength measured at 13 distances from the gantry along the Head–Foot (y-) axis. Field strength trace was computed by cubic interpolation. Negative distances represent regions within the scanner bore. The magnetic field was 3 T in the bore and field strength decayed rapidly as a function of distance from gantry. **B**, Maximum field strength differences computed over a sliding 14-cm segment, derived from (A). This function approximates the spatial variation in static field strength (in the y-axis) encountered by a TMS coil (see Materials and Methods). The markers denote field differences calculated for locations where TMS fields were measured (circle = B_0 field, square = fringe field near gantry, diamond = fringe field further removed from gantry). Inset scatterplot shows the relationship between static field variations and TMS field variations (indexed by the horizontal/vertical coil ratio). Filled and open markers correspond to high- and low-intensity TMS measurements, respectively. Larger static field differences corresponded with increased TMS field variation (i.e., smaller H/V ratios). 1 Tesla = 10^5 Gauss.