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Arm movement maps evoked by cortical magnetic stimulation in a robotic environment

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Abstract

Many neurological diseases result in a severe inability to reach for which there is no proven therapy. Promising new interventions to address reaching rehabilitation using robotic training devices are currently under investigation in clinical trials but the neural mechanisms that underlie these interventions are not understood. Transcranial magnetic stimulation (TMS) may be used to probe such mechanisms quickly and non-invasively, by mapping muscle and movement representations in the primary motor cortex (M1). Here we investigate movement maps in healthy young subjects at rest using TMS in the robotic environment, with the goal of determining the range of TMS accessible movements, as a starting point for the study of cortical plasticity in combination with robotic therapy. We systematically stimulated the left motor cortex of 14 normal volunteers while the right hand and forearm rested in the cradle of a two degree-of-freedom planar rehabilitation robot (IMT). Maps were created by applying 10 stimuli at each of 9 locations (3 × 3 cm grid) centered on the M1 movement hotspot for each subject, defined as the stimulation location that elicited robot cradle movements of the greatest distance. TMS-evoked movement kinematics were measured by the robotic encoders and ranged in magnitude from 0–3 cm. Movement maps varied by subject and by location within a subject. However, movements were very consistent within a single stimulation location for a given subject. Movement vectors remained relatively constant (limited to <90 degree section of the planar field) within some subjects across the entire map, while others covered a wider range of directions. This may be due to individual differences in cortical physiology or anatomy, resulting in a practical limit to the areas that are TMS-accessible. This study provides a baseline inventory of possible TMS-evoked arm movements in the robotic reaching trainer, and thus may provide a real-time, non-invasive platform for neurophysiology based evaluation and therapy in motor rehabilitation settings.

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Keywords

Motor Cortex; Mapping; Transcranial Magnetic Stimulation; Robotics

Transcranial magnetic stimulation (TMS) has long been used to probe and modify the primary motor cortex (M1, for recent reviews see: Reis et al. 2008; Ridding and Rothwell 2007). TMS mapping studies have demonstrated muscle somatotopy along the length of the central sulcus (e.g. Cohen et al. 1991; Singh et al. 1997), somatotopy for finger movements (Gentner and Classen 2006), and TMS has been used to elicit stereotyped thumb movements (Classen et al. 1998) involving precise muscle activation. However recent research has revealed that many muscle representations are more distributed and overlapping than commonly assumed (Schieber 2001; Beisteiner et al. 2001), such that selective activation of individual, isolated muscles with TMS may be impossible. Further confounding studies of individual muscle maps, surface electrical potentials generated in muscles (a method traditionally used to measure TMS effects on M1) are biased towards the most superficial fibers. Invasive recording techniques have been used to more directly study primate motor cortex, revealing multiple representations, including muscles and intended movements (Georgopoulos et al. 1992), but the study of multi-joint movement end points has not, to our knowledge, been undertaken. Such simple end point measurements are currently used as markers for functional improvement by therapists (e.g. reaching towards a cup on a table top, collecting change from a counter top) and in upper extremity end-effector type robots for arm rehabilitation (e.g. Aisen et al. 1997; Krebs et al. 1999). These robots provide an opportunity for precisely measuring such movements (Finley et al. 2005), as well as for *combining* TMS with practice of assisted reaching movements in potential *hybrid* rehabilitation methods.

Our goal in this study was to provide a baseline understanding of movement maps in healthy control subjects using TMS in the robotic training environment. This is a necessary first step towards using TMS in rehabilitation robots as a rapid, non-invasive measure of cortical plasticity in subjects with neuromotor deficits, and to measure how training may affect these maps. We were particularly interested in the range of movements that could be elicited, and how much control of movement direction could be achieved by changing the coil position, practical issues for the eventual application of TMS in combination with robotic reaching therapy.

Experimental Procedures

Subjects

Fourteen normal subjects were evaluated. They were recruited and provided informed consent in a protocol approved by the University of Maryland Institutional Review Board and local Veterans Administration Research Committee. Subjects ranged in age from 24–33 (mean 28 ± 3) years. All subjects were right-handed and all robotic mapping was performed with the right arm to avoid handedness and hemispheric complications in data evaluation.

Data Collection

Subjects were seated in front of a two degree-of-freedom planar robot (Interactive Motion Technologies, Inc., Cambridge, MA) with their arm in the horizontal plane and forearm horizontal at a 90° angle (Fig 1A). Subjects were instructed to rest their right forearm in the molded cradle of the robotic device, with their hand resting around the handle at the end of the cradle. Two straps fastened around the forearm to secure it in the cradle. Subjects were initially instructed, and repeatedly reminded, to relax their upper extremities. Electromyogram (EMG) signals from 4 right arm muscles (anterior deltoid (AD), posterior deltoid (PD), biceps brachii

(BB), and triceps brachii (TB)) were monitored to ensure subjects were at rest prior to stimulation. We chose these four muscles because they are considered principal contributors for elbow and shoulder movements (d'Avella et al. 2006), and recording from them did not interfere with privacy. The robot applied a spring-like centripetal force field (75 N/m) to prevent the arm/hand from drifting and to return to the initial configuration after each elicited movement, without any subject effort. The robot encoders recorded TMS-elicited movements in the horizontal plane.

Stimulation

TMS of the left (contralateral) motor cortex was performed using a MagStim 200 Magnetic Stimulator and figure-eight coil (MagStim Ltd., Wales, UK). During stimulation the figure-eight stimulating coil was held tangential to the scalp with the handle pointing backward and laterally at a 45 degree angle to the sagittal plane. Coil position and orientation relative to the subject's head were monitored and recorded using a frameless stereotactic system (BrainSight, Rogue Research, Montreal, QC), and were co-registered with an anatomical MRI image or standard brain template (Fig 1B). Stimulation was guided by a 1-cm grid distributed anteroposteriorly and mediolaterally over the brain surface in BrainSight (Fig 1B), initially centered over the hand knob of left M1.

Movement hotspots: were located for each subject by methodically stimulating each location in the grid over the representation of the right arm in the left motor cortex. The hotspot is defined as the location that, when stimulated, produced the largest movement recorded by the planar robot.

Movement thresholds: were determined individually for each subject by stimulating the movement hotspot and defined as the lowest stimulation level that elicited any visible movement in at least 5 of 10 stimulations.

Mapping Procedure

TMS pulses were applied at 120% of movement threshold in each of 9 (3×3) 1-cm spaced grid points centered on the movement hotspot (Fig 1B). Single-pulse TMS stimulation was applied 10 times (5 seconds between stimulations) at each location while movements were recorded by the robot.

Movement Vectors

Movements were recorded by the robot at 200 Hz. Movement vectors were calculated offline for each arm movement elicited by TMS stimulation from the starting position of the robot handle (pre-stimulation) to the point farthest from the starting position post-stimulation using custom LabVIEW software (National Instruments, Inc., Austin, TX). Direction and magnitude were calculated for each movement vector as follows:

$$M = \sqrt{x^2 + y^2}$$

$$\theta = \tan^{-1} \left(\frac{y}{x} \right)$$

where M is the magnitude, θ is the movement direction, x is the right+/left- position, and y is the forward+/backward- position of the robot handle as depicted in Figure 1B, leftmost panel.

Statistical Significance: was tested for movement direction and magnitude individually as well as combined using the X,Y coordinates. For direction and X,Y coordinates, we used the Watson-Williams test (an approximate ANOVA test for circular data, see (Watson and Williams 1956; Jammalamadaka and SenGupta 2001) for further examples and usage).

Magnitude comparisons were made using students' paired *t*-tests with a Bonferroni corrected *p*-value of 0.00625 used to correct for multiple comparisons ($p < 0.05$ corrected for 8 surround comparisons to center location). In one subject, multiple regression analysis of MEP amplitudes from each of the 4 recorded muscles (AD, PD, BB, TB) was performed against corresponding movements in the X,Y directions, with adjusted multiple R^2 value and the *p*-value of the regression ANOVA reported.

Results

Movement maps, consisting of 10 movement vectors at each of 9 cortical locations (Figure 1C, D) were recorded for 14 subjects. Stimulation strength (120% of movement threshold) ranged from 46 to 97% (mean = $71 \pm 18\%$) of maximal stimulator output. We analyzed the direction and magnitude of movements in the robotic environment elicited by TMS stimulation of motor cortex. (All recorded movements were TMS-elicited; no voluntary movements are reported here.)

We found that single pulse TMS over the left motor cortex produced measurable movements in the robotic environment for all subjects. TMS pulses elicited ballistic movements outward from the central holding spot (normalized start position) which then relaxed back towards center due to the spring-like robotic force field (see Methods). Figure 1C depicts movement trajectories elicited by stimulating the same location over 3 time points (0–50 minutes), demonstrating that movement trajectories are stable over time within subject, within location. Movement vectors for all nine stimulated locations (depicted for the entire 3×3 map for 2 example subjects, Fig 1D, E, cortical locations centered on the hotspot) were then used to quantify movement direction and magnitude for each subject.

We found no systematic variation in movement direction or magnitude by map location across our subject sample. Maps varied greatly between subjects, some having a broad range of different movements elicited by TMS across cortical locations, some having only one general movement (similar angle and magnitude) for all locations. An example of stimulation location-dependent variability is depicted in Figure 1D, while a very consistent map (movements were always directed left/up from center) is depicted in Figure 1E.

Mean movement vectors were computed for each stimulation location (location means: Figure 1F, G depicted by thin grey lines) as were subject mean vectors (averaged across all stimulation locations) for each of the 14 subjects (subject means: depicted by thick black lines). In all figures, the start of each mean vector is centered at (0,0) to emphasize disparity of magnitudes and directions across locations. The movement map for each subject can then be classified as either broadly tuned (mean directions spanning over 90 degrees as in Fig 1F) or narrowly tuned (mean directions falling within a single 90 degree quadrant as in Fig 1G). The subjects' map classifications split equally between these descriptive categories, with 7 broadly tuned and 7 narrowly tuned subject maps. (This classification was for descriptive purposes as data fell along a broadly/narrowly tuned continuum, not a dichotomous split.)

Movement magnitudes and directions are summarized in Figure 2. For each subject all individual movements are plotted as black dots (9 locations $\times$ 10 stimulations at each location = 90 individual movements per subject), with location means depicted as grey bars (3×3 grid = 9 map locations per subject) and subject means plotted as red diamonds. Movement *magnitudes* were small, ranging from 0.1 to 27.7 mm with mean $\pm$ standard deviation of 1.6 ± 1.7 mm and 6/14 subjects having TMS elicited movements greater than 5 mm (Fig 2A). Individual movement *directions* spanned the entire range [-180 to 180 degrees] (black dots, Fig 2B) across subjects (0 degrees = rightward, 90 = forward, away from body, $180/-180$ = leftward, $-90/270$ backward, towards body as diagrammed in Fig 1B). Subject means (red

diamonds) were most concentrated between 0–90 degrees (right/forward) with 10/14 subjects falling in this quadrant.

We further quantified movement map variability by determining how many of the eight surround locations were significantly different from the central location (movement hotspot) for each subject. The number of locations that significantly differed from center for each of these measures by subject is plotted in Figure 3A. No subject had all surround locations different from the center location, i.e., at least one of the 8 locations was similar to the center hot spot. Only one subject (subject #6, Fig 3A) had no significant differences between locations for direction, magnitude, or X,Y coordinates. On average (Figure 3B), we found that just over half of the surround stimulation location maps were of movements that differed significantly from the central hotspot (mean $\pm$ SEM of 4.1 ± 0.6), with contributing factors of differing direction (2.5 ± 0.5), magnitude (2.7 ± 1.7) or X,Y vector (2.1 ± 0.6). This finding suggests that the spatial separation of different movements, as accessible by TMS, is small.

EMG data was monitored for all subjects to insure that their arms were at rest prior to stimulation. While sufficient for this purpose, the majority of these proximal MEP were contaminated by long-lasting stimulus artifacts, and did not allow for a comprehensive quantitative analysis of motor evoked potentials (MEP) for all subjects. All four channels of EMG data were cleanly recorded for a single subject and are presented in Figure 4. MEP traces recorded from each muscle (AD, PD, BB, TB) were averaged over 10 stimulations for each cortical location (from 10 to 30 ms post-stimulus delivery). These means are plotted above the mean movement vector (black arrows) corresponding movements elicited at that location. We found some evidence of somatotopic gradients for individual muscles over the $3\text{ cm} \times 3\text{ cm}$ area of M1, but muscle representations as evidenced by EMG recordings were broadly distributed and overlapping. Using multiple regression analysis, we found that for this subject, the best predictor of movement along the medial/lateral (X) axis was the Biceps Brachii (regression ANOVA, $p < 0.1$), which, while significant, explained less than 20% of the variance (Adjusted Multiple $R^2 = 0.187$). Movement along the anterior/posterior (Y) axis was best explained by a combination of Biceps Brachii and Triceps Brachii (regression ANOVA, $p < 0.01$), which together explained less than 30% of the variance (Adjusted Multiple $R^2 = 0.298$). The remaining variance is likely due to muscles from which we did not record. TMS elicited movements may result from complex activation of multiple muscles and EMG recordings may not be able to capture the movement variance no matter how many sites are recorded from since they are biased to surface muscle fibers.

Discussion

The data presented here define for the first time a map of arm movements that can be elicited by TMS in a two degree-of-freedom horizontal plane. Robotic devices operating in the horizontal plane are now commonly used in both research and rehabilitation. The characterization we provide below of the movement maps that can be elicited by TMS may be used as a basis for rapid, non-invasive, TMS-analysis of robotic intervention-induced plasticity in motor cortical networks. We analyzed the direction and magnitude of movements elicited by surface stimulation of motor cortex in healthy subjects and found that a wide range of movement maps in the robotic environment are elicited by TMS. The type and range of movements, however, vary considerably by subject, and by stimulation location within a subject. In some cases movements were stereotyped despite changes in stimulus location.

Mapping studies of the primary motor cortex have shown a general somatotopy and demonstrated that individual muscles can be isolated in a location dependent manner (Graziano et al. 2002). However, muscle maps show a high degree of overlap; multiple muscles within a region may be simultaneously activated by cortical stimulation and similar movements may

be elicited by stimulating separate regions of cortex, complicating the interpretation of these muscle maps (see (Gentner and Classen 2006) for a thorough analysis of these and other considerations in TMS induced hand movements). Further, despite years of intense scrutiny, there continues to be discussion about the features represented in M1, i.e. whether they are individual muscles, postural primitives, or movement sequences (Scott 2008). Our single subject EMG findings presented in Figure 4 suggest that, as expected, different muscles contribute differently to different endpoint movement vectors, and can be used to explain a portion of the variance in movement. But the majority of movements we recorded cannot be predicted based on EMG activation patterns alone (>70%) and the same movement can be evoked by activation of different muscles. More extensive surface EMG recordings may not be able to access *all* of the information necessary to predict movements (Anderson and Fuglevand 2008) and such data may be highly variable by individual (Staudenmann et al. 2008).

Studies of voluntary reaching have revealed that muscle activation is more understandable in terms of muscle synergy patterns (d'Avella et al. 2006d'Avella et al. 2008.) It appears from our work that TMS may predominantly activate a particular movement synergy, generally an outward reach, explaining the high degree of consistency in movements in some individuals. This also explains the fact that MEP do not reliably correlate with movement end points, as individual muscle activity may not be cortically represented. The selection of one movement synergy over another appears to be more difficult with TMS than with voluntary activation, at least in the resting state.

By focusing here on the movement end-effector (final handle position of the planar robot), we cannot determine what spatio-temporal pattern of which muscle activations are responsible for the movement, but we can precisely define maps of functional end points. Though simplified, such end point measurements may be extremely useful, both to therapists in their functional training and evaluation, and to robotic devices currently being tested in clinical trials.

One possible explanation for the between subject variability in maps is individual differences in cortical physiology or anatomy that may result in a practical limit to the areas that are TMS-accessible. The range of movements accessible may be an important factor in determining whether or not an individual is a good candidate for TMS-based therapeutic interventions. Alternatively, it may be that physiological state determines the direction of the elicited movement (Gary and Thompson 2009; Lang et al. 2004), in which case there may be opportunities to manipulate that state and access a wider movement repertoire.

Though shown to be stable within a subject over time with no intervention (Malcolm et al. 2006), TMS muscle maps have also been found to be plastic, i.e., they can be altered by repetitive practice (Befisch et al. 2000; Krutky and Perreault 2007; Rosenkranz et al. 2007). We anticipate that the movement maps we have defined in this study are subject to similar plasticity. Repetitive training paradigms (robotic or other) may alter these maps, and they may do so differentially for subjects with different initial map parameters (for example, broadly or narrowly tuned subjects may respond differently to training paradigms). We are currently using TMS mapping to investigate the cortical effects of a robotic training paradigm.

Data collected here are limited by the mapping of 3-D movements to a 2-D plane. To gain a more complete understanding of the full range of TMS-evoked movements, we would need to use a three-degree-of-freedom robotic device. Such devices are currently in development (for example: ARMin (Nef and Riener 2007); MIME (Lum et al. 2002); Haptic Master (Van der Linde et al. 2002)), but none are currently in clinical trials for rehabilitation therapy like the IMT planar robot utilized in this study which is commercially available and already in wide spread use. Analysis of 2D maps such as in this study may be useful in determining populations

that may benefit from a particular intervention, as a basis for evaluating the best dosing of a particular intervention, as well as suggest potential cortical mechanisms underlying training-induced functional changes for future investigation.

After further investigation of the variability in healthy young subjects (through manipulation of cortical ‘state’ via practice movements, joint position analysis, EMG analysis, and 3-D robotic environments as mentioned above) differences between elderly/young subjects should be examined to see how TMS-evoked movement maps may change with age. Once a more thorough baseline understanding of TMS-elicited movement maps in the robotic environment is established, we can begin to evaluate how motor cortical movement representations are altered in various disease states (e.g. stroke, traumatic brain injury or Parkinson’s disease) and quantitatively investigate how different training paradigms affect the motor cortex. TMS mapping of motor cortex can be used as an effective tool to investigate motor cortical contributions to upper extremity movements in the robotic environment and the efficacy of training paradigms on motor cortical plasticity.

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List of Abbreviations

TMS	transcranial magnetic stimulation
M1	primary motor cortex
EMG	electromyogram
MEP	motor evoked potential
AD	anterior deltoid
PD	posterior deltoid
BB	biceps brachii
TB	triceps brachii
ANOVA	analysis of variance
2-D, 3-D	2, 3-dimensional

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Figure 1.

(A) Experimental setup: Subjects were seated in front of a two degree-of-freedom planar robot (Interactive Motion Technologies, Inc., Cambridge, MA) with their upper arm in the horizontal plane and forearm horizontal at a 90° angle (Fig 1A) and instructed to rest their arm in the cradle, relaxing all muscles of the upper extremity. (B) Example of hotspot (pink, #1) and surround (orange, #2–9) grid locations for an individual subject. All subject 3×3 grids for were similarly located over the hand region of the contralateral motor cortex. Stimulation locations were guided by a grid of anteroposteriorly and mediolaterally oriented 1 cm squares drawn over the brain surface in Brainsight, resulting in map of 9 locations (3×3 centered on hotspot) for each subject. Movement directions (X,Y coordinates, and angles in degrees) are depicted

in schematic of experimental setup as viewed from above. **(C)** Example of TMS elicited movement trajectories in the X,Y plane, with all movements beginning at the same starting point (0,0). Hotspot stimulation at three different time points illustrates that movement maps are stable over time (0–50 minutes) with no significant changes in direction or magnitude. **(D, E)** Movement maps vary by location and by subject, although movements made by stimulating the same location were generally of similar magnitude and direction. Maps could differ by location within a subject (D, both magnitude and direction vary by location) or remain fairly constant (E, direction remains similar across all locations in the map). **(F, G)** Subject means reveal differences in both movement magnitude and direction. Location mean vectors were created (*thin grey lines*) for each location on the map (9 total), then subject mean vectors were created from these location means (*thick black lines*). Half of the subjects had broad, dispersed maps (F) and half had very narrow, directionally consistent maps (G).

A) Movement Distance

B) Movement Direction

Figure 2.

Movement magnitude and direction were broadly distributed between and within subjects. Magnitude (A) and direction (B) of each movement are depicted individually (*black dots*), by mean movement for all 10 stimuli given at a single cortical location (*grey bars*), and by mean movement for a single subject over all 9 cortical stimulation locations (*red diamonds*). Movements ranged in magnitude from 0–30 mm, mean < 5mm. Movements were elicited in most all directions, with subject means ranging from –45 to +180 degrees (in body centric coordinates, 0=movement to the right, +90=away from trunk, ±180=left, –90=towards the trunk).

A) Surround Maps Significantly Different from Center Map

B) Mean Map Differences within Subject

Figure 3.

Surround maps differed from central map in majority of comparisons. Map differences (map resulting from stimulation at the center of the 3×3 grid compared to maps resulting from stimulation at the 8 surround grid locations) were found in both magnitude and direction and varied by subject (A). Subjects had on average 2 surround maps (of 8 possible) that differed from the center map significantly by direction and 2 that differed significantly by magnitude. (B) Significant differences were found in >50% of maps tested.

Figure 4.

EMG activity map by stimulation location (locations 1 and 2 labeled as in Figure 1), all plotted from 0–30 msec post stimulation. Mean movement vectors (5 mm scale bar) elicited by TMS at each stimulation site are plotted (black arrows) below the corresponding mean EMG recordings (10–30 msec/0.5 mV scale bars apply to all locations) for 4 muscles: AD = anterior deltoid, PD = posterior deltoid, BB = biceps brachii, TB = triceps brachii. EMG traces are averages over 10 trials from 10–50 msec post stimulus for each muscle. Muscle activation patterns did exhibit some somatopy, but also showed a high degree of overlap, such that movement vectors could not be predicted by EMG activity in these four muscles.