J Rehabil Med 2003; Suppl. 41: 20–26

TRANSCRANIAL MAGNETIC STIMULATION TO ASSESS CORTICAL PLASTICITY: A CRITICAL PERSPECTIVE FOR STROKE REHABILITATION

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Transcranial magnetic stimulation has gained increasing visibility as an evaluative and interventional tool during the past 15 years. Within the context of rehabilitation, transcranial magnetic stimulation has been applied to differentiate excitatory and inhibitory mechanisms and to assess cortical reorganization following specific interventions. This article reviews some of the more salient features of transcranial magnetic stimulation applications relevant to stroke rehabilitation, highlighting the strengths and weaknesses in this approach. Data derived from such studies may be profoundly over-interpreted. Information is provided showing the importance of utilizing fundamental principles of electrode placement and kinesiological electromyography to more accurately reflect and interpret data emerging from transcranial magnetic stimulation mapping studies, particularly as they apply to the interpretation of cortical reorganization following application of neurorehabilitative procedures.

Key words: upper extremity, forced use, constraint-induced movement therapy

J Rehabil Med 2003; suppl. 41: 20–26.

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INTRODUCTION

Transcranial magnetic stimulation (TMS) was introduced by Barker and colleagues in 1985 (1) and has since gained recognition as a safe, relatively painless and noninvasive method for mapping cortical motor representation, both in normal and pathologic cases (2–7). Recently, TMS has been used to investigate the possible mechanisms underlying both spontaneous and therapy-induced post-stroke motor recovery.

TMS is based upon the principle of electromagnetic induction. Electrical current is directed through a hand-held copper-stimulating coil, with the consequent production of a transient magnetic field. When held over the scalp, the rapidly changing magnetic field induces a small electrical current in underlying brain tissue, producing a depolarization of nerve cells resulting in the stimulation or disruption of brain activity. When performed over the primary motor cortex at low stimulus intensities, TMS is thought to stimulate the corticospinal tract indirectly (transsynaptically) via horizontal fiber depolarization (8, 9). The resultant efferent volleys can then be recorded as motor-evoked potentials (MEPs) via surface or indwelling electrodes at peripheral target muscles.

TMS may be applied as a single stimulus or repeated many times per second, with variation in intensity, site and orientation of the magnetic field. The brain response produced with TMS will depend on all of these variables as well as the shape of the stimulating coil. In most studies, either round or figure-of-8 coils are used. Figure-of-8 coils consist of two round coils placed side by side, producing more focal stimulation. Coils with a reduced diameter have a more focused field of stimulation but require greater stimulation intensity to produce similar depth of field penetration. Highly focused stimulation is essential for many research applications although uncertainty exists about whether this property will prove clinically useful, when less focused stimulation may better compensate for variation in location of pathological lesions and inter-individual anatomy.

The delivery of TMS is often described by the frequency of the cortical stimulation. Rapid rate or repetitive TMS (rTMS) usually refers to the application of TMS at frequencies above 1 Hz and is often applied in treatment studies. TMS at 1 Hz and below may be referred to as slow or low frequency TMS and is often used in mapping procedures (10).

Different TMS parameters are used to investigate motor system excitability. The resting motor threshold intensity is the lowest stimulator output intensity applied with the target muscle in a relaxed state that can induce MEPs of a least 50 μV peak-to-peak amplitude in at least 50% of up to ten trials (11). Other important measures include the location of the "hot spot" (the most active scalp position for the target muscle), the excitability threshold (measured at the hot spot), the area of motor output representation, the MEP latency, the amplitude-weighted center of gravity (CoG) (4), MEP amplitudes (at rest and sometimes with facilitation) and MEP recruitment curves (12–14).

This article reviews therapeutic studies where TMS-evoked motor mapping has been applied in rehabilitation. We examined strengths and weaknesses in this approach as they relate to our interpretation of cortical reorganization following application of neurorehabilitative procedures.

DOI 10.1080/16501960310010106

THE EMERGENCE OF TMS TO EVALUATE MOTOR REORGANIZATION AFTER STROKE

Several investigators have examined the correlation between TMS-evoked motor map characteristics after stroke and the extent of motor recovery in humans (15–17). Pennisi et al. (18) demonstrated that complete hand paralysis in association with absence of early MEPs (within 48 h of ictus) predicted poor neurologic recovery at one year in 15 subjects post-stroke (middle cerebral artery infarct). Conversely, the preservation of TMS evoked MEPs in the early post-stroke period may portend good functional recovery (9, 19). Other investigators have reported relationships between the rate and extent of post-stroke recovery and changes in the following: presence of MEP, conduction time from cortex to muscle, MEP latency, excitability threshold and MEP amplitude (9, 18, 20, 21). In mono-hemispheric infarctions, decreased affected hemisphere (AH) motor output area and increased excitability thresholds for paretic muscles have been repeatedly observed in TMS-derived maps performed in post-stroke patients during the sub-acute and chronic phases (22, 23). These electrophysiologic changes are presumably related to the motor impairment and may be secondary to neuronal damage, disuse, unbalanced transcallosal inhibition from the less affected hemisphere, or other unidentified mechanisms (24).

RESPONSE TO REPETITIVE TASK PRACTICE

Results from recent work with animal models have suggested that the specificity and difficulty of training may impact the extent of use-dependent cortical plasticity (25–28). Similar findings have been reported in motor recovery in human subjects post-stroke. Leipert et al. (23) examined the effect of one intensive session of physical therapy in 9 subjects, 4-8 weeks post-stroke. Participants received 1.5 h of manual dexterity exercises, in addition to ongoing "standard" therapy. TMS mapping of the abductor pollicis brevis (APB) representation was performed one week before, immediately before, immediately after and one day after the training session. Measures of motor output area, excitability threshold at the APB hot spot, (location at which an evoked muscle response greater than 50 μV in amplitude is seen at minimal stimulus intensity), and CoG for the APB muscle of the AH and unaffected hemispheres (UH) did not significantly change between the two pre-training measures, indicating that significant changes did not occur because of spontaneous recovery or nonspecific training. The area of APB representation in the AH area increased significantly immediately after training, but then decreased toward baseline after one day. Increased AH motor output area was associated with improved dexterity on a clinical measure (the Nine Hole Peg Test) in 7 of the subjects, although the amount of clinical improvement did not correlate with the extent of change in area. The excitability threshold at the hot spot and the CoG were unchanged after training, possibly signifying that enlargement in the AH area was due to increased excitability at the edges of the map. The rapid change detected in the TMS-derived maps after brief training epochs suggests that functional, rather than structural, mechanisms were involved. Potential mechanisms discussed include the modulation of inhibitory GABA-ergic transmission at the borders of the motor map and alteration in glutamate transmission (23). Classen et al. (12, 29) have suggested that the "motor cortex builds up, and then loses, in a short time, memory traces of movements retaining the subject's recent history of performance" (29, p. 168).

TMS MAPPING IN CONSTRAINT-INDUCED THERAPY

Recent studies have employed TMS motor mapping to investigate the effect of constraint-induced (CI) movement therapy for the more affected UE. Liepert et al. (30) used focal TMS to construct cortical output maps to the APB in 6 chronic stroke patients before and after 10 days of CI therapy. As noted in prior studies of post-stroke subjects, significantly higher motor thresholds, smaller amplitudes and a smaller area of excitable cortex were observed in the AH. After CI therapy, TMS parameters showed no change in thresholds, but significant increases in MEP amplitude and APB motor output area in the AH, possibly indicating increased excitability of surrounding neuronal networks. The UH output areas were smaller after the training period, presumably because of decreased use of the less affected UE, normalization of the UH APB representation, or increased transcallosal inhibition of the UH by the AH. CoG shifts were significant (in the mediolateral axis) only for the AH, suggesting possible recruitment of adjacent areas along the motor cortex. All subjects improved significantly in their use of the affected extremity, but scores on the Motor Activity Log (MAL), a six-point subjective impression of how well and how often movement is observed in the affected arm during basic activities of daily living, did not correlate to the degree of map change. The Leipert group suggests that "physiotherapy induces use-dependent reorganization which supports recovery-associated plastic changes" (23, p. 321).

In another study (22), clinical (MAL) and TMS measures were made at multiple time points before and after CI therapy in 13 chronic stroke patients. Neither baseline measure showed appreciable change at 2 weeks and 1 day prior to CI therapy, suggesting little spontaneous recovery and good test-retest reliability. Again, the AH showed a smaller APB representation area at baseline, with a near doubling of the area post-CI therapy. MAL improvements were maintained at the later measurement points. However, a return toward baseline in the AH APB representation area was seen at the 4 week and 6 month TMS sessions, indicating a possible "normalization after therapy-induced hyper-excitability" (22, p. 1214) via improved synaptic efficiency or the relegation of motor function to TMS-inaccessible regions.

EXAMINING MECHANISMS TO EXPLAIN TMS MAP CHANGES

Changes in cortical motor representation areas have been documented in TMS mapping investigations of motor recovery after stroke with and without specific therapeutic intervention. Suggested mechanisms for these map changes can include: i) resolution of edema and removal of necrotic tissue after CNS injury (31); ii) restitution of damaged pathways (22); iii) modulation of GABA-ergic intracortical inhibition (22, 32, 33); iv) changes in synaptic efficacy (22, 29); v) alteration of transcallosal inhibition (22); vi) substitution from ipsi-lesional parallel pathways (22, 34); vii) activation of ipsilateral (contra-lesional) pathways (30); viii) short-term potentiated responses after terminating repetitive stimulation (29); and ix) long-term potentiation (13, 35).

ALTERNATIVE EXPLANATIONS FOR OBSERVED CHANGES IN MAP AREA

Changes in the excitable surface area derived from TMS-evoked motor maps to an individual muscle have been linked to changes in motor function and interpreted as a reflection of alterations in the cortical representation for that muscle. However, the measured surface area of these TMS maps seems to exceed the likely cortical volume that is dedicated to a single muscle representation, or even a single movement. Thickbroom et al. (36) employed excitability curves at each scalp location that elicited responses in the first dorsal interosseous and found that the shape of the curves remained similar at each scalp site (with a similar slope and saturation level), but was shifted along the intensity axis. This finding suggests that a small population of motor cortical neurons, perhaps deeply situated, may be stimulated by current spread with gradually less responsiveness as the TMS coil is moved away from the epicenter of the representation. Therefore changes in the surface area may represent increased excitability to current spread, without reflecting a true expansion or contraction of the cortical representation area. The center of the map may be a more stable measure of map change, and should be included in future mapping studies. A few recent TMS mapping studies in post-stroke subjects have revealed medio-lateral shifts in the CoG associated with improvements in motor function of the target muscle (22, 30).

CRITICAL ASSESSMENT OF MEPs AS THEY RELATE TO FUNCTIONAL CHANGE

The degree of reproducibility of TMS-evoked motor maps is a key issue when attempting to detect subtle plastic changes in a given individual or when comparing results from different laboratories; yet, few investigators have studied this question. So far, reproducibility has been accessed in terms of the variability of the amplitude of the evoked response (7), the amplitude and latency of the response as well as the area of the map (3), the location and area of the map (5) and its area, volume and average amplitude of the evoked response (24).

One critical area that has been overlooked is the relationship of electrode placements to the specificity of muscle response and subsequent interpretation of data. Often TMS mapping experiments do not describe the details of surface electrode placement (4, 7, 37, 38). Traditionally surface electromyograms (EMG) are recorded with silver-silver chloride electrodes using a tendon-belly montage in which the active electrode is placed over the belly of the muscle and the reference electrode over the interphalangeal joint of the muscle being tested or other bony landmark. This type of electrode placement has been described for TMS mapping for many muscles of the upper extremity including the: APB (5, 22, 24, 39–41), abductor digiti minimi (ADM) (24, 42, 43), first dorsal interosseous (36, 44), ADM (5, 45), and extensor digitorum communis (EDC) (46).

Use of the belly-tendon method has a distinguished history, emanating from evoked muscle responses to peripheral nerve stimulation, at which time the emphasis is simply in examining responsiveness of many muscles to estimate nerve-to-muscle integrity. However, when determining functional recovery in many intrinsic muscles or larger muscle masses, such as the forearm extensors, there may be increased concern over electrode placement.

Stroke survivors often have impairment upon attempting volitional movement into extension (out of flexion synergy) to grasp and reach for an object. Thus, when exploring responses from a muscle functionally relevant to regaining the ability to manipulate objects in the environment, such as the EDC, there are disadvantages to using the montage placement.

For the more detailed study of connections to muscles relating to function, a “close-spaced” electrode placement may be preferred. By using a close-spaced recording electrode array, the clinician can better relate the functional movement to the specific action of the underlying muscle, thus leading to a better determination (understanding) of the mechanisms observed following an intervention.

To examine this contention carefully, MEP amplitudes from a wide-spaced electrode array were compared to a close-spaced electrode array from the same forearm muscle in a normal healthy individual. The MEPs were recorded using two 7×4 mm silver-silver chloride surface electrodes (Medtronic, Inc., Minneapolis, MN). The interelectrode distance for the close-spaced electrode array was approximately 1.5 cm, while the wide-spaced array was approximately 18 cm. The skin surface over the EDC on the forearms was shaved and abraded with alcohol until an erythemic response appeared. Recording electrodes were placed on the skin over the EDC muscle bellies (close-spaced array) and EDC muscle belly and ulnar head (wide-spaced array). A ground electrode was applied ipsilaterally and proximally to the recording electrodes at the level of the olecranon process of the ulna, to reduce EMG

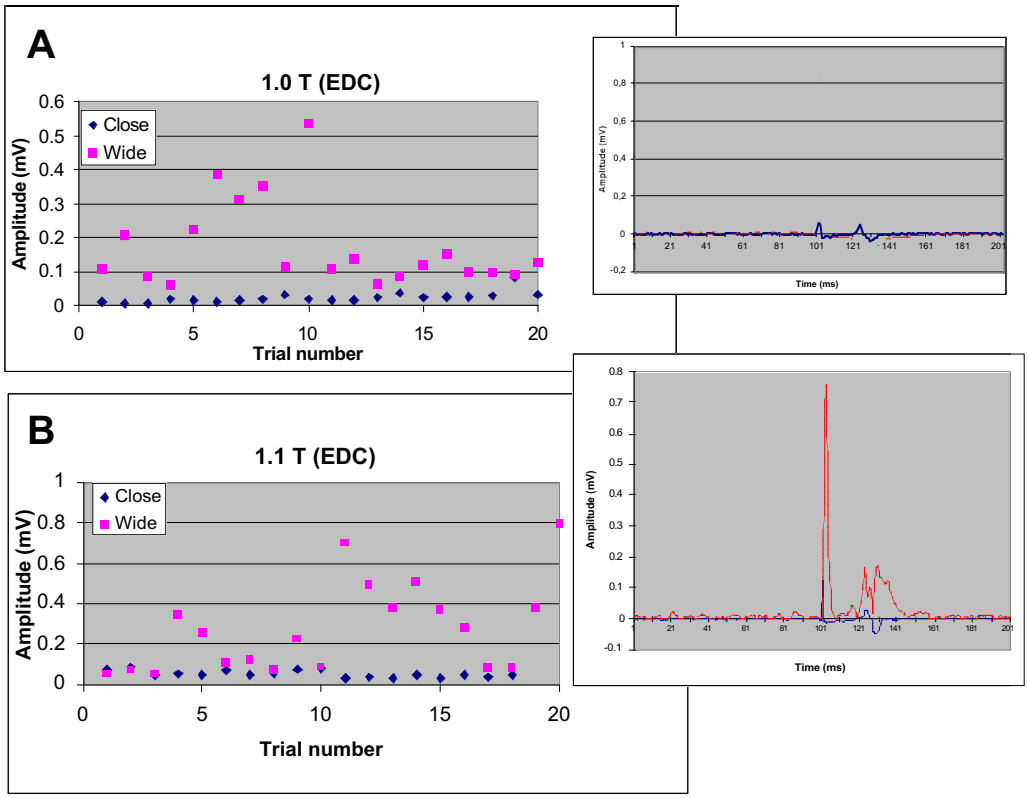

Fig. 1. Amplitude of extensor digitorum communis (EDC) motor-evoked potential (MEP) at motor threshold *(A)* and 110% motor threshold *(B)* in 20 trials for one subject. Diamonds represent closely spaced electrode array, while squares represent widely spaced electrode array. Inserts in upper right corner denote a representative MEP of a single trial from the subject, with the light trace derived from the wide spaced electrode array. Note reduced sensitivity at 1.1 threshold (T).

noise levels. Skin impedance between recording electrodes, measured with an ohmmeter (Simpson 260 series 8, Simpson Electric Co., Elgin IL), was kept below 5 kilo-ohms (KK).

The study was performed with a 70 mm figure-of-8 coil using a single MAGSTIM 200 stimulator (Magstim Company Ltd., Whitland, Dyfed, UK) and delivered in a systematic fashion at approximately 0.2 Hz. The magnetic coil was oriented tangentially to the scalp, with the handle of the coil in line with the sagittal plane. EMG signals were amplified (×1000) using a James Long Isolated Bioelectric Amplifier (SA Instrumentation Company, Encinitas, CA) and band-pass filtered (10–1000 Hz) before being digitized at 1000 Hz for 200 ms following each stimulus. Further signal processing, analysis and storage were performed using a PC system containing custom-established routines created in LabView 6.0 (National Instruments, Austin, TX). An audio amplifier was used to monitor pre-activation EMG activity from each EDC muscle to assure minimal muscle activity prior to stimulation.

The scalp overlying the motor cortex was stimulated at motor threshold (1.0 T), while recording MEPs from EDC. As expected larger MEP amplitudes were consistently observed for the wide placed electrode array when compared to the closely spaced electrodes (Fig. 1A). Some potentials recorded from the widely spaced arrangement used by Wittenberg et al. (47) were considerably larger than the accompanying close-spaced array. We also observed larger average MEP amplitude, area under the curve and root-mean-square voltage with wide-spaced electrodes (Fig. 2).

MEP is more variable at lower stimulus intensities and variability in MEP size is a direct function of the proportion of motoneurons in the total pool recruited by each cortical stimulus. Therefore the same protocol was repeated using stimulus intensities of 110% of motor threshold (1.1T), as is commonly done in TMS studies (22, 30). At higher stimulus intensities there are more motoneurons stimulated and, therefore, fewer are available to spontaneously reach threshold and discharge. Again, larger MEP amplitudes were observed for the wide-placed electrode array when compared to the closely spaced electrodes (Fig. 1B). When averaged over twenty trials a similar pattern was observed for MEP amplitude, root-mean-square voltage and area under the curve (Fig. 3).

The intention of mapping the evoked responses in EDC to TMS of motor cortex is to gain insight into changes in finger extensor representation following specific therapeutic interventions for patients with stroke. This concern is particularly relevant since training should focus on improving motor control by stressing selective (out-of-synergy) movement patterns (48). Wider electrode placements, including those used in a study on EDC (47), may actually record motions, such as finger and wrist flexion, that are counterproductive to the very therapy being instituted. This possibility was confirmed by recording surface EMG overlying EDC while performing finger flexion/extension and wrist adduction/abduction.

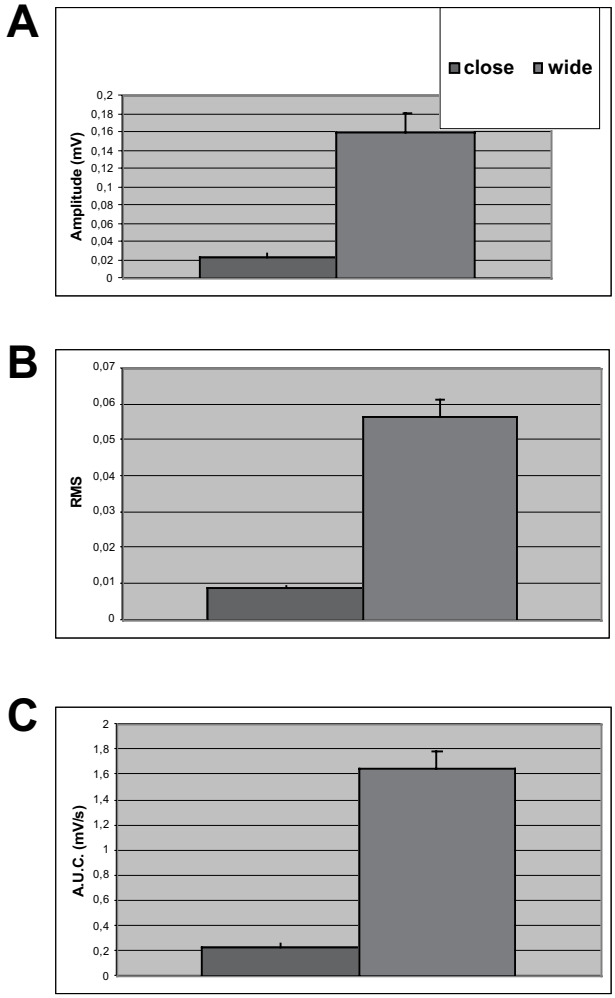

Fig. 2. Average transcranial magnetic stimulation response characteristics at 1.0 threshold for extensor digitorum communis as a function of inter-electrode distance over 20 trials. Motor-evoked potential Amplitude (A), root mean square (RMS) (B) and area under curve (AUC) (C). The bars indicate standard error.

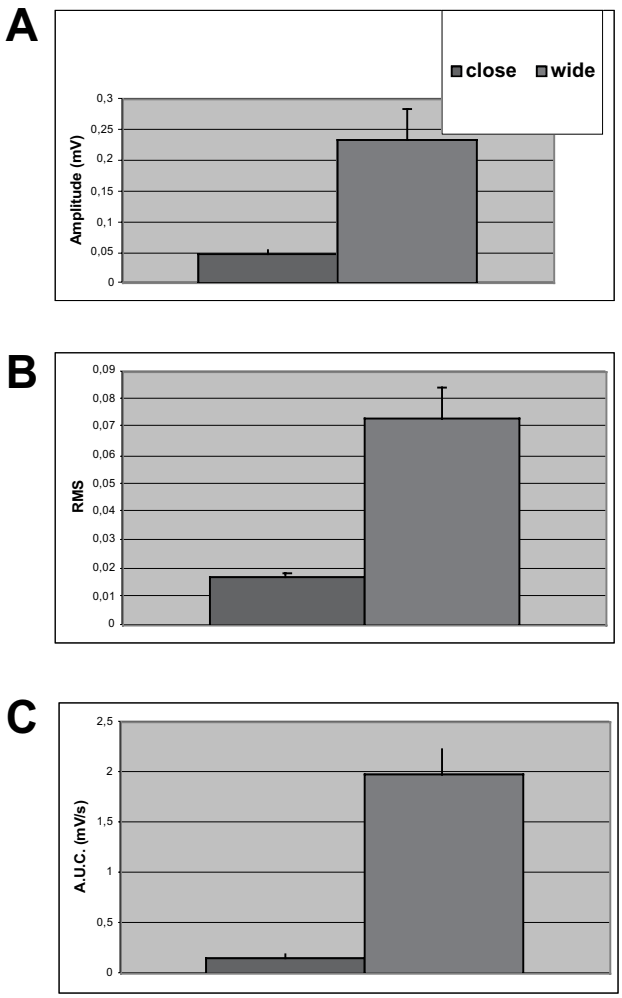

Fig. 3. Average transcranial magnetic stimulation response characteristics at 1.1 threshold for extensor digitorum communis as a function of inter-electrode distance over 20 trials. Motor-evoked potential Amplitude (A), root mean square (RMS) (B) and area under curve (AUC) (C). The bars indicate standard error.

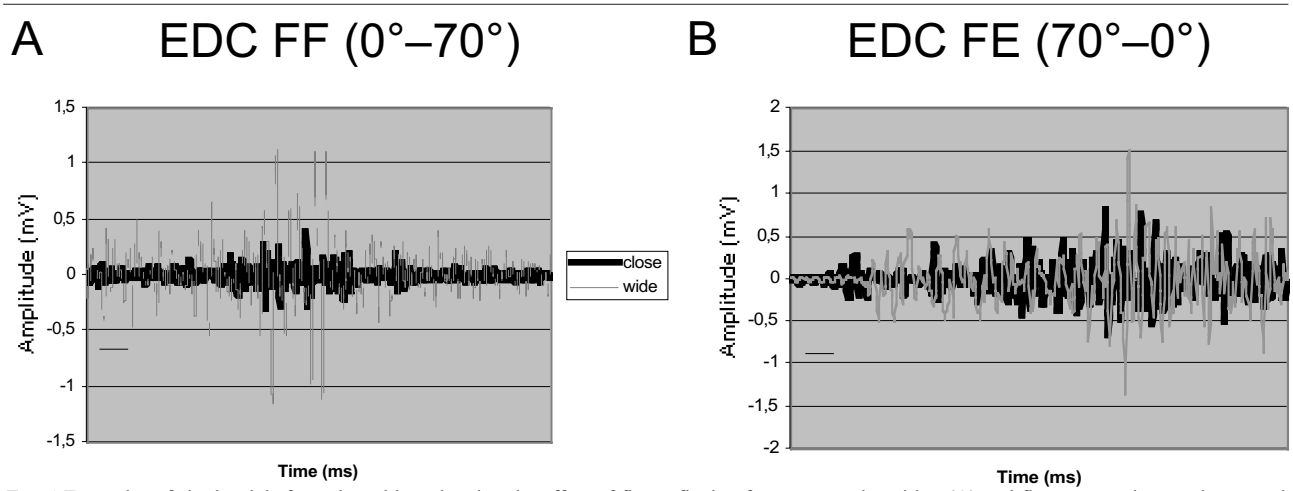

Fig. 4. Examples of single trials from the subject showing the effect of finger flexion from a neutral position (A) and finger extension to the neutral position (B) on extensor digitorum communis electromyographic activity. Traces from close spaced (thick-dark line) electrode arrays are superimposed on traces from wide spaced (thin-light line) electrode arrays for comparison.

During finger flexion (0°–70°) and extension (70°–0°), large EMG responses in EDC in the widely spaced compared to the closely spaced electrode array were observed (Fig. 4). Comparable disparities were seen in EDC in the widely spaced electrode array during wrist adduction and abduction over a 20 degree range from neutral, suggesting that the wide-spaced electrode array records activity for sagittal plane wrist movements and not just finger extension.

Additional studies are needed in which electrodes are arranged on previously mapped muscles such as the ADM, APB, and first dorsal interosseous, to secure greater isolation of specific movements. These studies would facilitate a clearer interpretation of the relationship of a TMS-evoked motor map to the movement in question on the one hand and the functional relevance of that change to the intervention being evaluated, on the other. Only then can those muscles' TMS derived motor map results be compared to the outcomes found in this study.

ACKNOWLEDGEMENT

This work is supported in part by NIH Grant HD 37606.

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