

Distribution and Latency of Muscle Responses to Transcranial Magnetic Stimulation of Motor Cortex After Spinal Cord Injury in Humans

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ABSTRACT

Noninvasive transcranial magnetic stimulation (TMS) of the motor cortex was used to evoke electromyographic (EMG) responses in persons with spinal cord injury ($n = 97$) and able-bodied subjects ($n = 20$, for comparative data). Our goal was to evaluate, for different levels and severity of spinal cord injury, potential differences in the distribution and latency of motor responses in a large sample of muscles affected by the injury. The spinal cord injury (SCI) population was divided into subgroups based upon injury location (cervical, thoracic, and thoracolumbar) and clinical status (motor-complete versus motor-incomplete). Cortical stimuli were delivered while subjects attempted to contract individual muscles, in order to both maximize the probability of a response to TMS and minimize the response latency. Subjects with motor-incomplete injuries to the cervical or thoracic spinal cord were more likely to demonstrate volitional and TMS-evoked contractions in muscles controlling their foot and ankle (i.e., distal lower limb muscles) compared to muscles of the thigh (i.e., proximal lower limb muscles). When TMS did evoke responses in muscles innervated at levels caudal to the spinal cord lesion, response latencies of muscles in the lower limbs were delayed equally for persons with injury to the cervical or thoracic spinal cord, suggesting normal central motor conduction velocity in motor axons caudal to the lesion. In fact, motor response distribution and latencies were essentially indistinguishable for injuries to the cervical or thoracic (at or rostral to T10) levels of the spine. In contrast, motor-incomplete SCI subjects with injuries at the thoracolumbar level showed a higher probability of preserved volitional movements and TMS-evoked contractions in proximal muscles of the lower limb, and absent responses in distal muscles. When responses to TMS were seen in this group, the latencies were not significantly longer than those of able-bodied (AB) subjects, strongly suggestive of "root sparing" as a basis for motor function in subjects with injury at or caudal to the T11 vertebral body. Both the distribution and latency of TMS-evoked responses are consistent with highly focal lesions to the spinal cord in the subjects examined. The pattern of preserved responsiveness predominating in the distal leg muscles is consistent with a greater role of corticospinal tract innervation of these muscles compared to more proximal muscles of the thigh and hip.

Key words: cortical magnetic stimulation; EMG responses; human spinal cord injury; motor-complete and -incomplete injury

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INTRODUCTION

A NUMBER OF CLINICAL TESTS have been developed to categorize the neurological or functional status of persons after spinal cord injury (SCI). With respect to volitional movements, results of such tests are typically expressed as a numeric index, representing the composite contribution or action of functional muscle groups (Klose et al., 1980; Ducker et al., 1982; Bracken et al., 1990; Brown et al., 1991). Other evaluation tools emphasize a person's functional capabilities, including activities of daily living (Ditunno, 1992; Davis et al., 1993; Daverat et al., 1995; Mizukami et al., 1995; Wells and Nicosia, 1995) or gait (Frankel et al., 1969; Waters et al., 1989; Crozier et al., 1992). Such measures have allowed comparison within and between groups to help in the evaluation of different treatment and rehabilitation strategies (Frankel et al., 1969; Tator et al., 1987; Bracken et al., 1990; Geisler et al., 1991; Krengel et al., 1993), but provide limited insight into the physiologic properties of spinal motor pathways subserving volitional movement caudal to the injury site.

Spinal cord injury does not typically result in a complete discontinuity of neuronal tissue at the lesion's epicenter. In the histopathology series from Bunge et al. (1997), approximately 65% of traumatic SCI cases demonstrated some amount of axonal sparing across the lesion. Behavioral evidence indicates that at least some spared fibers in many survivors of spinal cord injury are functional, and the incidence of "incomplete" injury is rising (Schwab and Bartholdi, 1996), now accounting for more than 50% of the SCI population admitted to our acute treatment center (Calancie, unpublished observations; Waters et al., 1995). Studies of the physiologic properties of such spared axons, particularly those associated with motor control, are limited in number and scope (Thompson et al., 1987; Topka et al., 1991; Brouwer et al., 1992; Hayes et al., 1992; Lewko et al., 1995). Of particular interest to us is the physiologic basis for the recovery of volitional movements in muscles initially left completely paralyzed by a spinal cord injury. Improved understanding of the factors underlying such recovery might help guide development of the most appropriate intervention(s) for persons who have sustained a spinal cord injury.

In the present study, we examined central motor conduction properties using a combination of voluntary contractions and noninvasive transcranial magnetic stimulation (TMS) of the motor cortex (Barker et al., 1987). Both the distribution and latency of TMS-evoked responses in numerous upper and lower limb muscles were studied. Subjects included a large population of persons with SCI of different levels and severities, most of whom had sus-

tained their injury at least 1 year prior to study (i.e., they were "chronic"). Our goals were twofold: (1) establish a database for persons with chronic injury against which we could compare results from serial studies in persons with acute injuries; and (2) determine whether alterations in conduction properties of central motor axons were confined to the region of injury, or were instead distributed caudal to the injury site. Portions of this study have been presented elsewhere (Calancie, 1995).

METHODS

Subjects

Studies were conducted on 97 persons with a history of spinal cord injury and on 20 able-bodied (AB) subjects for comparative data. Exclusion criteria were based on our use of TMS for motor cortex stimulation. They included a history of seizures, brain injury, stroke, implanted metal device in the cranium (including aneurysm clip), or implanted biomedical device (e.g., cardiac pacemaker). Many subjects with cervical SCI had posterior cervical wiring or anterior cervical instrumentation (e.g., Caspar plate) for bony stabilization, yet all were studied with TMS without incident. All subjects gave their informed consent for this study, which was approved by the Human Ethics committee of the University of Miami.

Subject age varied between 15 and 71 years (32.9 ± 11.3 years for SCI; 30.8 ± 12.2 years for AB), and height varied between 4'9"-6'6" (SCI) and 5'2"-6'4" (AB). Eighty-two percent of the SCI subjects were male, in keeping with the much higher incidence of SCI in males. Seventy-five percent of the AB group was male. Data are included from 17 SCI subjects who were examined within 2–12 months postinjury. Only subjects whose spinal cord injury was a result of acute trauma were included. The causes of injury, including the percent of the total population injured in that manner, are as follows: motor vehicle accident (48%), diving (16%), sports-related (13%), gunshot wound (9%), fall (7%), and other (7%, including crush, decompression sickness, and surgical trauma).

For statistical comparisons, the level of orthopedic injury was used to divide subjects into subgroups, as follows: group 1, cervical (C1–T1); group 2, thoracic (T2–T10); and group 3, thoracolumbar (T11–L2). The distribution into subgroups by level of injury, as a percentage of the total sample population, was as follows: group 1 (cervical), 76%; group 2 (thoracic), 14%; and group 3 (thoracolumbar), 10%. Subjects who had some voluntary movement in one or both lower limbs at the time of our TMS-based studies are referred to as motor-incomplete (i.e., Frankel C, D, or E). Persons with cervical injuries that may have left them with limited move-

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ments in the distal upper limbs (i.e., within the zone of injury, defined as three neurological segments caudal to the last normal level (American Spinal Injury Association, 1987), but with no lower limb movement(s), were categorized as motor-complete (i.e., Frankel A or B), for the purposes of this study. Using this nomenclature, 64% of subjects with SCI were judged to be motor-incomplete. Sensory testing, including that within the S4 and S5 segments, was not routinely done, precluding classification of subjects by the American Spinal Injury Association (or International Standards) criteria (Ditunno et al., 1994). Approximately one-third of the SCI subjects were currently taking antispasmodic medications at the time of our examination. Some subjects were studied with TMS on more than one occasion. In those cases for which the same muscle was examined, only those data from the most recent evaluation are presented. Repeated studies of the time-course of motor recovery after SCI using the methods described below will be the focus of a separate report.

Instrumentation

Transcranial magnetic stimulation of motor cortex was delivered with a Cadwell MES-10 magnetic stimulator equipped with a "pointed" coil (outer diameter = 9.5 cm), whose center was positioned tangentially along the midline, approximately 1. cm anterior to C_z. This stimulation arrangement provides more widespread recruitment of muscles in both upper and lower limbs compared to the more selective "butterfly" coil, even when the latter coil is optimally positioned over specific areas of the motor cortex (Calancie, unpublished observations). Pairs of surface disc electrodes were used for electromyographic (EMG) recordings (1 cm diameter, 3–5-cm spacing) in most subjects (>90%), while noninsulated electroencephalography (EEG)-type subdermal electrodes placed under the skin were used during preliminary studies. These two electrode configurations gave results indistinguishable from one another (e.g., see Hugon, 1973; Nuwer et al., 1993). EMG signals were preamplified close to the source, filtered and amplified (100 Hz to 5 kHz; 1- or 10-K gain), and stored on magnetic tape after being digitized (Vetter 4000AS). EMG signals were displayed on a computer monitor (RC Electronics Computerscope) and simultaneously processed through audio mixers (Rane RM 26) connected to a loudspeaker for audio feedback of individual or multiple EMG channels.

As many as 12 channels of EMG were recorded simultaneously. Muscle identities were chosen to provide an overview of flexors and extensors of the upper and lower limbs, as well as intrinsic muscles of the hand and foot. They included biceps brachii (Biceps), triceps

brachii (Triceps), wrist flexors [including flexor carpi radialis (FCR)], wrist extensors [including extensor carpi radialis (ECR)], thenar muscles of the hand [including abductor pollicis brevis (APB)], hypothenar muscles of the hand [including abductor digiti minimi (ADM)], quadriceps (QUADS), hamstring (HAMS), hip adductors (ADD), tibialis anterior (TA), Soleus (SOL), and abductor hallucis (AbH).

In AB subjects, EMG responses to TMS were recorded from left side muscles only. In SCI subjects, we typically recorded from six pairs of muscles bilaterally; hence, not all muscles named above were studied at one time in SCI subjects. Consistent with other studies on persons with SCI, responses from left- and right-sided muscles were treated as independent measures, since the underlying disorder is due to a lesion that does not necessarily affect the left and right sides of the spinal cord equally (Bracken et al., 1990; Waters et al., 1993; Ditunno et al., 1994) and is not due to a systemic disease process (Segura et al., 1992).

Protocol

Subjects were seated comfortably in a semireclining position. They were asked to attempt an isolated voluntary contraction in each of the muscles being recorded from, and were given visual and auditory feedback of just that muscle's EMG. Subjects were discouraged from making widespread contraction efforts as a means of facilitating the muscle contraction being attempted. For example, some subjects would, at the initiation of a contraction, take a deep breath and perform a Valsalva maneuver while simultaneously attempting to contract the muscle in question. Others would use their arms to redistribute their weight on the chair, or to push down on their thighs. These maneuvers could elicit lower limb spasms in some subjects, making differentiation between volitional and reflex muscle recruitment virtually impossible.

After completing the voluntary contractions, the "threshold" TMS intensity was determined (defined for this study as the minimum stimulus intensity needed to elicit a response in >50% of trials from an upper limb (APB) and lower limb (AbH) target muscle with the subject at rest). For AB subjects, the stimulus intensity was then increased from this threshold level by 10–20% of the device maximum, and TMS was applied while the subject attempted to contract each muscle in turn (i.e., facilitate that muscle's motoneuron pool). The stimulus intensity used for these trials was 50–70% for upper limb muscles and 70–90% for lower limb muscles. For more than 90% of the SCI subjects, we used 100% stimulus intensity for evaluating all muscles, to maximize the

probability for evoking responses to TMS. Stimulus intensities of 90% were used for the other SCI subjects, as they found 100% intensities to cause excess discomfort.

Based on computer display of the EMG waveforms, if there was a visible but poorly defined evoked response to TMS, up to 10 stimuli were delivered while testing that muscle. If the muscle being examined showed a well-defined response from trial to trial, then three to five cortical stimuli were delivered. If there had been no EMG from a given muscle during voluntary contractions and no response was seen with two cortical stimuli when the subject was attempting to contract that muscle, no additional stimuli were applied for study of that muscle. This variability in numbers of stimuli presented for different muscle groups was done in order to minimize the subject's discomfort, while ensuring that through rectification and signal averaging, small responses to TMS might be resolved from background EMG in that muscle. The total number of stimuli delivered in a given session varied from a low of approximately 30 to as many as 130 TMS pulses.

Analysis

All EMG analysis was conducted off-line from the tape-recorded records. Data were digitized (RC Electronics Computerscope) at a 5-kHz sampling rate for each channel. All TMS-evoked EMG records were rectified and averaged for each muscle being examined. Typically, the amplitude of the TMS-evoked EMG was largest when that muscle was being facilitated with a background contraction at the time of stimulation, but considerable variability in response amplitude was seen from trial to trial, even when attempting to keep all variables constant (e.g., stimulus intensity, background contraction level, duration of resting period between stimuli). We have previously reported such variability in EMG amplitude of evoked motor responses to transcranial motor cortex stimulation (Calancie et al., 1987), as have others (Rothwell et al., 1987; Berardelli et al., 1991; Kiers et al., 1993). Therefore, we did not attempt to quantify the magnitude of the evoked response (e.g., peak-to-peak amplitude, or area). Instead, TMS-evoked responses were simply categorized as being either Present or Absent. Criteria for this determination included an appropriate latency (i.e., onset not less than minimum latencies for AB subjects and not greater than two times the minimum AB latency) and minimum amplitude. Responses were considered Present when the maxima of the averaged evoked responses exceeded approximately 20 μ V with respect to the averaged, baseline activity. The same two investigators (N.A. and S.S.) made determinations of response category (Present or Absent) and onset latency for the experiments re-

ported herein. These investigators were unaware of the clinical status (motor-complete versus motor-incomplete) of the majority of research subjects at the time the motor responses were analyzed, reducing the possibility of bias in data interpretation.

The minimum TMS-evoked response latency of a given muscle group was determined with cursors from the averaged record of rectified EMG. For AB subjects, the response latencies for biceps, FCR, APB, QUADS, TA, and AbH were correlated with subject heights. Similar correlations were made for SCI subjects in groups 1 and 2. Response latencies for SCI subjects were expressed both in absolute terms, and as a difference between the measured latency for that subject's particular muscle and the average latency for that muscle from AB subjects. This difference is termed the response delay. We did not correct these "delay" values for subject height (see Results).

Nonparametric χ^2 analyses were used to compare the incidence of response category (Present versus Absent) between different lower limb muscles in each of the cervical (group 1), thoracic (group 2), and thoracolumbar (group 3) subgroups of motor-incomplete subjects (i.e., within-group comparisons between muscles). χ^2 analyses of response category incidence for the same muscle between the motor-incomplete populations were also carried out (i.e., between-group comparisons of the same muscle). Results were considered significant at the 0.05 level. All analyses were done with Statistica, a PC-based software package.

To test whether all muscles innervated by segmental levels within or caudal to the zone of spinal cord injury would have prolonged minimum latencies to TMS, one-way analysis of variance (ANOVA) was used to compare minimum absolute response latencies across the three subgroups with SCI and the AB group (i.e., four groups in total). To test for differences in TMS-evoked response latency within SCI subgroups, a multivariate ANOVA comparing response delays across subgroups and muscles was carried out. When a significant effect was found ($p < 0.05$), Tukey honest significance difference (HSD) posttest comparisons were made.

Each subject's evaluation included an attempted maximum voluntary contraction in each muscle studied, prior to initiation of the TMS trials. When subjects were able to produce a contraction, this led to a brief period of EMG waveforms associated with that contraction attempt. We assigned a numeric score to this interference pattern, as described elsewhere (Alexeeva et al., 1997). We have found that the EMG interference pattern measured in this manner is positively and significantly related to the force produced as judged by a physical therapist through manual muscle testing (in preparation and reported in abstract

form in Calancie, 1995). The EMG score was therefore treated as an indication of the degree of volitional recruitment capable for that muscle. An overall multivariate analysis of variance (MANOVA) was used to test whether muscles with better clinical recruitment (i.e., higher EMG scores) demonstrated shorter TMS-evoked response latencies. For this comparison, the quadriceps (proximal) and abductor hallucis (distal) were included.

RESULTS

Most subjects found the experience of TMS to be unpleasant when stimulus intensities exceeded 80% of the device maximum, yet all subjects tolerated the protocol without ending it prematurely. Approximately 20% of the subjects reported minor headache, which developed either during or shortly after completing the evaluation; this incidence is higher than reported previously (Eisen and Shtybel, 1990), although the present study protocol resulted in considerably more stimuli at average intensities higher than those used by Eisen and Shtybel (1990). Otherwise, there were no adverse reactions to TMS, in agreement with recent reports (Chiappa, 1994; Chokroverty et al., 1995).

Representative TMS-Evoked Responses: AB and SCI Subjects

Figure 1 illustrates motor responses to TMS in a male AB subject. Responses were seen in each of the muscle groups examined in this subject, although those in the Triceps, ADD, HAMS, and Soleus muscles were poorly defined. Because we could not confirm that EMG activity measured by the hip adductor electrodes (ADD) did not include contributions from quadriceps or hamstring muscle groups, we chose to eliminate adductor records from further analysis (Phillips and Park, 1991). Of the upper limb muscles studied in AB subjects, triceps brachii responses were poorly defined in four subjects. Nearly all other upper limb TMS-evoked responses and 100% of the responses in the hand muscles examined were large and well defined in the AB subjects. Poorly defined TMS-evoked responses were seen more frequently in lower limb muscles of AB subjects, particularly for the soleus muscle, in keeping with other studies (Brouwer and Ashby, 1992; Nielsen et al., 1993; Valls-Solé et al., 1994). In one AB subject, TMS stimulation failed to recruit the soleus muscle at all (i.e., its response was absent).

Figure 2 shows representative, TMS-evoked EMG records from two SCI subjects, both with injury to the cervical cord. The upper records (Fig. 2A) illustrate left- and right-sided responses from a motor-complete subject.

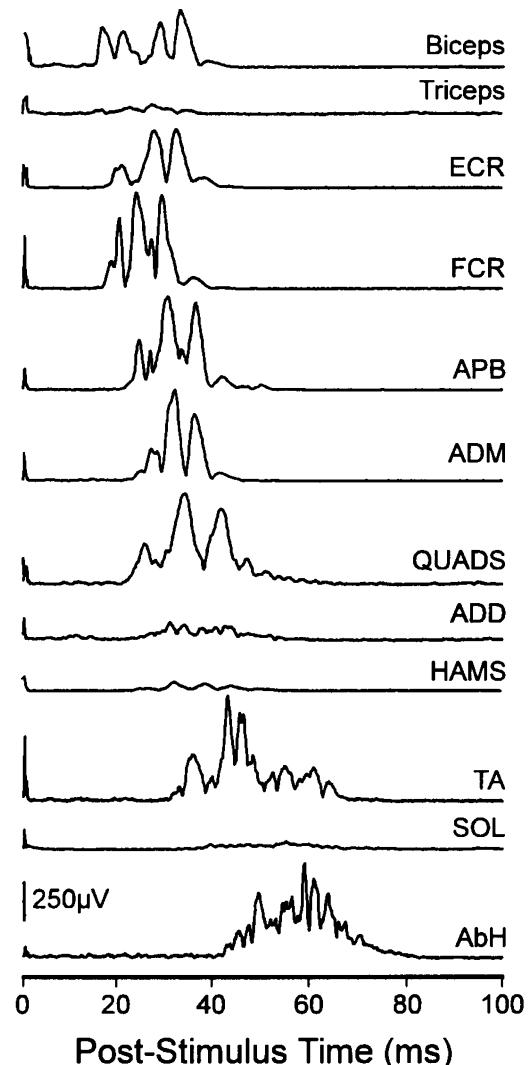


FIG. 1. Example of motor responses to TMS in an able-bodied (AB) subject. Each record shows the averaged ($n = 5$), rectified EMG response of a muscle while the subject is maintaining a weak voluntary contraction of that muscle at the time the stimulus is delivered. The responses were not recorded simultaneously but they were aligned at time "0", which corresponds to the delivery of the stimulus in this and subsequent figures. In this example, the stimulus intensity was 50% and 60% of the maximum stimulator output for upper and lower limb muscles, respectively.

Muscles in the upper limbs innervated within the zone of injury (i.e., FCR bilaterally and left APB) responded to TMS in this subject, although the left APB response was poorly defined. In the right APB for this subject, what appears to be EMG beginning at approximately 70 msec poststimulus is actually movement artifact of the APB electrode wires, resulting from strong biceps contraction and elbow flexion. (We confirmed this by affixing the

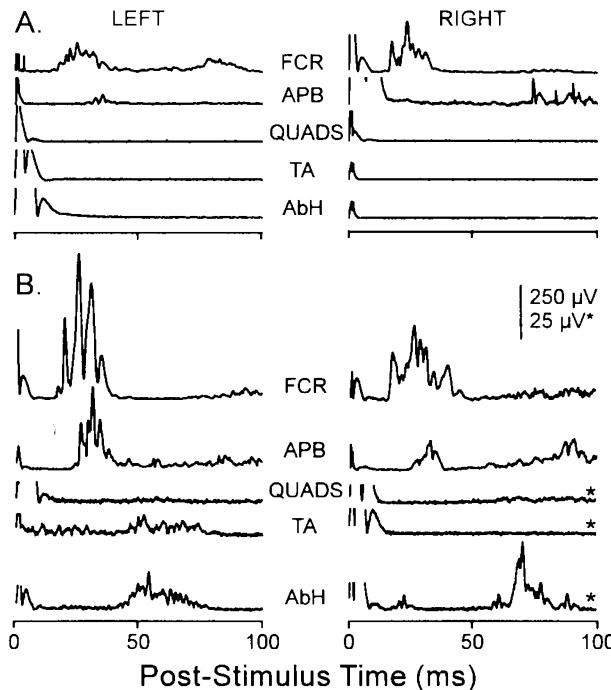


FIG. 2. Representative motor responses to TMS in two SCI subjects with a motor-complete (A) and motor-incomplete (B) lesion. “Left” and “right” indicate the side recorded from. The stimulus intensity was 90% in A and 100% in B. Note the different vertical calibration (*) for records from lower limb muscles in B.

APB electrode wires to the wrist, eliminating movement artifact during subsequent TMS applications. Care must be taken during the later periods after TMS, i.e., >60 msec, when some muscles may be actively shortening, to avoid misinterpreting movement-related artifacts, particularly when high amplification of EMG is used. Because this study concentrated on only short latency responses, and we were aware of the potential for artifacts caused by movement of electrode wires, the risk that our findings were contaminated by movement artifact is considered to be remote.) There was no sign of TMS-evoked EMG in this subject’s lower limb muscles.

EMG records from a motor-incomplete subject (Frankel C) are shown in Fig. 2B. In this case, TMS evoked a small but reproducible response in the left TA muscle and the AbH muscles bilaterally. No response was seen in the right TA or in the quadriceps bilaterally. Asymmetry in minimum latency can be seen in the AbH responses of Fig. 2B, where the onset of the evoked response in the right AbH was at approximately 65 msec, roughly 20 msec later than the left-sided AbH response latency in this motor-incomplete subject.

Threshold Intensity for TMS

When other factors are kept constant, such as the orientation of the stimulating coil and state of muscle relaxation, the minimum intensity of transcranial magnetic

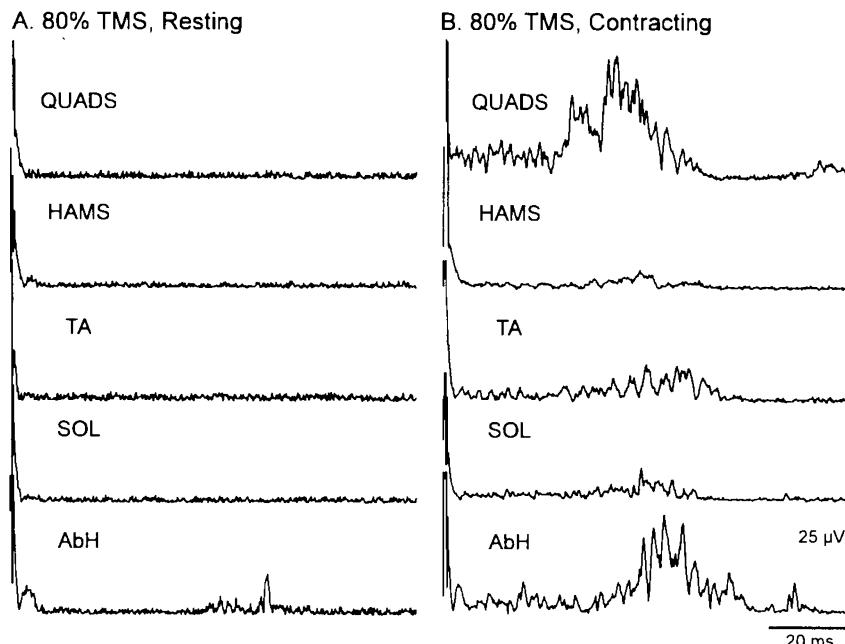


FIG. 3. Effect of voluntary contraction on TMS-evoked responses. (A) Subject relaxed in all muscles at time of TMS application. (B) Subject attempting to contract the target muscle at the time of TMS application. Records of rectified EMG are averaged from five individual trials in each case.

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stimulation needed to evoke a motor response (i.e., the threshold) can provide an indication of the extent to which corticospinal tract influence is acting on a given motoneuron pool (Furby et al., 1992; Lemon, 1995; reviewed in Mills and Nithi, 1997; and see Calancie et al., 1998). In the present study, the average minimum TMS intensities needed to evoke threshold responses in upper limb muscles were 59.8% ($\pm 15.0\%$) and 62.8% ($\pm 14.0\%$) for motor-complete and motor-incomplete SCI subjects, respectively. For purposes of comparison, the mean threshold for TMS-evoked motor responses in AB subjects was 48.8% ($\pm 6.4\%$) for upper limb muscles. For muscles within the lower limbs of motor-incomplete SCI subjects, the mean threshold for evoking responses was higher ($78.4 \pm 14.7\%$). In AB subjects, the threshold values for lower limb muscles were always higher than for upper limb muscles, but specific values for each subject were not established. Although there were ex-

ceptions, the APB muscle in the upper limb and the AbH muscle in the lower limb were the most easily-recruited by relatively weak intensities of TMS (i.e., these muscles had the lower thresholds) compared to more proximal muscles in the upper and lower limbs. This was true for both AB and motor-incomplete SCI subjects.

Figure 3 shows representative EMG records from right-side lower limb muscles of a motor-incomplete SCI subject (Frankel D) when tested with TMS while at rest (Fig. 3A) and while making a weak contraction at the time of stimulation (Fig. 3B) in each of the target muscles shown. At the threshold intensity while resting (80%), only the subject's AbH muscle responded to TMS. In contrast, each muscle was recruited by TMS when stimuli were superimposed on a background contraction in that target muscle (Fig. 3B). The volitional contractions in each muscle can be seen by the increased baseline "noise" following stimulus artifacts and prior to the

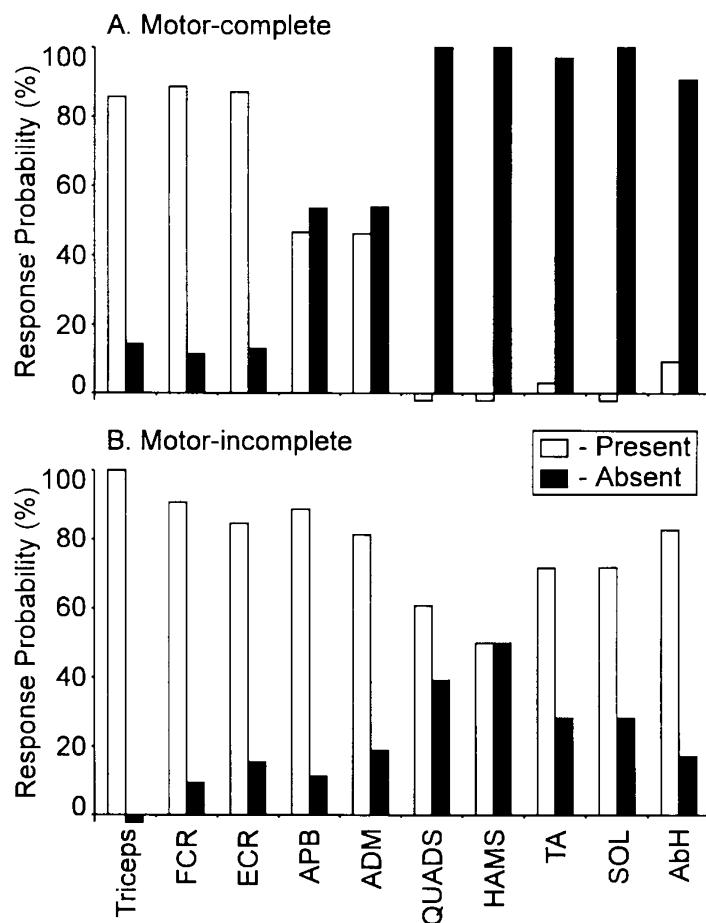


FIG. 4. TMS-evoked response probability (Present versus Absent) of each muscle tested for motor-complete (A; $n = 35$) and motor-incomplete SCI subjects (B; $n = 53$). Cases for which the response probability was zero are indicated by a slight down-going bar in this and the following figure.

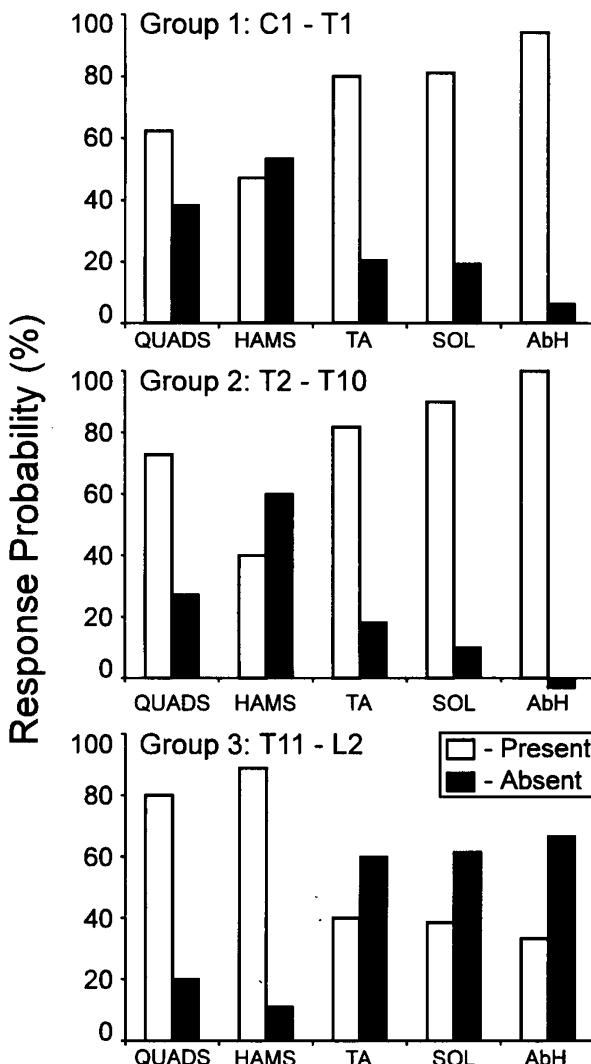


FIG. 5. TMS-evoked response probability (Present versus Absent) in motor-incomplete SCI subjects with a cervical injury (top; group 1, $n = 39$), thoracic injury (middle; group 2, $n = 7$), or thoracolumbar injury (bottom; group 3, $n = 7$).

evoked response in the averaged records of Fig. 3B. For the HAMS record in Fig. 3B, there was a barely discernible increase above the background activity, but a clear diminution of activity during the later period of the record (i.e., ~ 70 msec after the stimulus). This “silent period” (Calancie et al., 1987) is indicative of a short-latency effect of the cortical stimulus on the target muscle’s motoneuron pool, although the duration of the TMS-evoked silent period in clinically weak muscles is often relatively brief in persons with SCI (Calancie, unpublished observations).

Response Distribution and Probability

Eight of the subjects in this series had a particularly mild form of cervical spinal cord injury resulting in the central cord syndrome (CCS; Schneider et al., 1954; Quencer et al., 1992; Levi et al., 1996). The distribution of TMS-evoked responses in these subjects was exactly like that of AB subjects, whereas TMS-evoked response latencies were consistently prolonged. For these reasons, we have reported findings from subjects with central cord syndrome separately (Alexeeva et al., 1997) and excluded results from these subjects from further analysis in the present paper.

Figure 4 illustrates the distribution, by percent of total numbers of observations, of Present and Absent responses to TMS, as grouped by muscle and neurologic category (motor-complete and motor-incomplete) in the remaining SCI subjects. There was a near-uniform absence of response to TMS in lower limb muscles of motor-complete subjects (Fig. 4A), consistent with our definition of motor-complete. However, a small but reproducible EMG response was evoked by TMS in a total of five lower limb muscles in four motor-complete subjects. We found that these subjects could cause recruitment of one or two motor units during isolated voluntary contractions of these muscles, although no joint movement or muscle twitching was evident. Application of TMS during these voluntary contractions resulted in a small evoked motor response which could be recorded from the background activity through averaging.

TABLE 1. WITHIN-GROUP COMPARISONS OF TMS-EVOKED RESPONSE PROBABILITY (PRESENT VERSUS ABSENT) FOR EACH MUSCLE TESTED

	HAMS	TA	SOLEUS	AbH
Group 1 (cervical)				
Quads	NS	SIG	SIG	SIG
Hams	—	SIG	SIG	SIG
TA	—	—	NS	SIG
Soleus	—	—	—	SIG
Group 2 (thoracic)				
Quads	NS	NS	NS	$p = 0.06$
Hams	—	SIG	SIG	SIG
TA	—	—	NS	NS
Soleus	—	—	—	NS
Group 3 (thoracolumbar)				
Quads	NS	SIG	SIG	SIG
Hams	—	SIG	SIG	NS
TA	—	—	NS	NS
Soleus	—	—	—	NS

SIG, significant ($p < 0.05$); NS, not significant.

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Both upper and lower limb TMS-evoked responses were examined in persons with injury to the cervical spine, whereas only lower limb responses were studied in persons with thoracic or thoracolumbar injuries. For persons with cervical SCI, the probability of observing responses to TMS in the majority of upper limb muscles was relatively high in both the motor-complete and motor-incomplete populations studied. Not surprisingly, motor-incomplete subjects had a higher probability of having preserved responses to TMS in hand muscles (APB and ADM) compared to persons with motor-complete injuries (compare Fig. 4A with 4B). Note also from Fig. 4 that distal lower limb muscles were more likely to respond to TMS than proximal muscles in the motor-incomplete subjects.

Figure 4B was plotted from all motor-incomplete subjects, without considering the level of injury. When grouped by injury level, however, the distributions of TMS-evoked responses differed considerably between motor-incomplete subjects, as illustrated in Fig. 5. In subjects with cervical or thoracic spinal cord injuries (i.e., groups 1 and 2), proximal lower limb muscles (QUADS and HAMS) were less likely to respond to TMS, whereas distal lower limb muscles—particularly the AbH—were more likely to respond to TMS. Conversely, for persons with thoracolumbar lesions, the opposite pattern was evident: TMS-evoked responses were far more commonly observed in proximal muscles compared to distal muscles. These within-group differences between proximal and distal muscle response to TMS were, for the most part, statistically significant, as summarized in Table 1. For comparisons of a given muscle's TMS-evoked response probability between groups, Table 2 shows that there was no significant difference between any of the muscles for cervical (group 1) and thoracic (group 2) injury populations, but group 1/group 3 and group 2/group 3 comparisons by muscle revealed significant differences in most instances. Thus in those persons who had either recovered or retained voluntary movement of at least one

muscle in the lower limb after SCI, the TMS-evoked response probability for distal muscles was relatively high in persons with injury to the spinal cord proper, and relatively low in persons with injury to the base of the spinal cord (i.e., conus medullaris and/or cauda equina). Conversely, proximal muscles were more likely to respond to TMS in motor-incomplete subjects whose injury was to the caudal spinal cord, and less likely to respond in persons with more rostral injuries.

Data from Fig. 5, as well as the statistical analyses presented above, demonstrate the relatively greater degree of preserved TMS-evoked responses in distal musculature in persons with motor-incomplete cervical or thoracic spinal cord injury. However, one cannot determine from Fig. 5 to what extent there might be individual exceptions to this pattern. To address this point, Fig. 6 summarizes data from all motor-incomplete subjects from whom EMG from all of the QUADS, TA, SOL, and AbH muscles was recorded simultaneously in response to transcranial magnetic stimulation. When one or more muscles in a lower limb was (were) recruited by TMS in group 1 or group 2 subjects, the AbH was always included; in the population studied, there was not a single exception to this finding. In contrast, there were frequent trials in which there was no TMS-evoked response in AbH in persons with motor-incomplete injury to the thoracolumbar region of the spine (group 3), whereas responses in the QUADS were present in all but one case for these individuals.

The high probability of TMS-evoked activity in the hamstring muscles of group 3 subjects was unexpected. To rule out the possibility that quadriceps EMG was being picked up by the relatively distant hamstring electrodes (i.e., "cross-talk"), we reexamined each of the hamstring responses to TMS in group 3 subjects and confirmed that cross-talk was unlikely to be responsible for the TMS-evoked EMG records we observed. To illustrate, Fig. 7 shows data records for voluntary and TMS-evoked contractions in an individual from the group 3

**TABLE 2. BETWEEN-GROUP COMPARISONS OF
TMS-EVOKED RESPONSE PROBABILITY (PRESENT
VERSUS ABSENT) FOR EACH MUSCLE TESTED**

	<i>GRP 1 vs. GRP 2</i>	<i>GRP 1 vs. GRP 3</i>	<i>GRP 2 vs. GRP 3</i>
Quads	NS	NS	NS
Hams	NS	SIG	SIG
TA	NS	SIG	SIG
Soleus	NS	SIG	SIG
AbH	NS	SIG	SIG

SIG, significant ($p < 0.05$); NS, not significant.

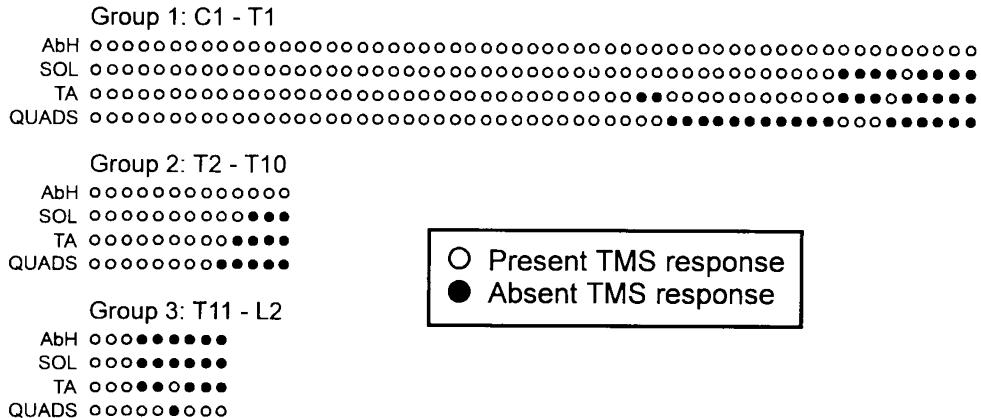


FIG. 6. Individual records of TMS-evoked response category (Present versus Absent) in all those cases for which EMG was recorded simultaneously from each of the quadriceps, tibialis anterior, soleus and abductor hallucis muscles in motor-incomplete subjects, grouped by level of injury as indicated.

motor-incomplete SCI population. This person had sustained an L1 burst fracture in a motor vehicle accident 8 years previously. At the time of testing, he was able to ambulate at speeds up to 2 miles/h, using Lofstrand crutches and bilateral ankle-foot orthoses. Examples of EMG activity during attempted voluntary contractions of each of three muscle groups (Fig. 7A-C) and as evoked by TMS (Fig. 7D,E; 100% stimulus intensity) are shown. This subject had difficulty recruiting quadriceps in complete isolation during voluntary contractions; such attempts typically led to modest levels of hamstring activity (Fig. 7A). Conversely, he was able to achieve almost complete isolation in contraction of the hamstring group

(Fig. 7B). Transcranial magnetic stimulation typically caused simultaneous recruitment in both QUADS and HAMS muscle groups. However, the relative size of the evoked response was influenced considerably by the subject's background contraction efforts at the time of stimulation, indicating at least partial independence of output from these two motoneuron pools. None of his AbH, TA, or soleus muscles showed voluntary or TMS-evoked EMG activity at any time in this evaluation (TA and soleus records not shown). Records in Fig. 7 help emphasize another finding which was very consistent throughout this study. That is, TMS-evoked responses were observed only in those muscle groups in which the

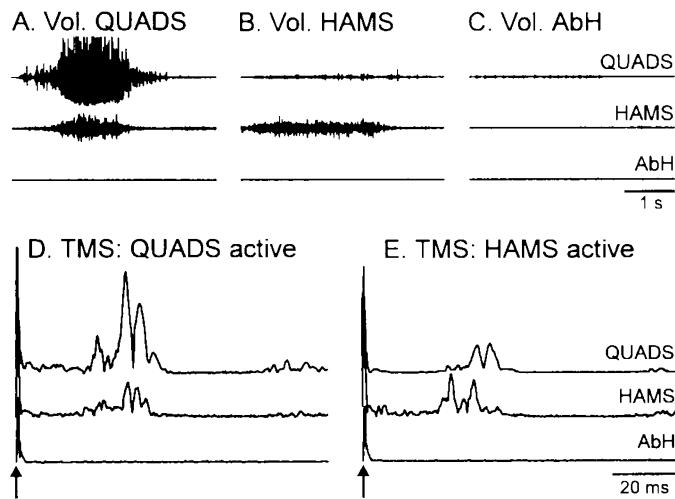


FIG. 7. EMG from each of the quadriceps, hamstring and abductor hallucis muscles during individual, voluntary contractions of the quadriceps (A), hamstring (B), and abductor hallucis muscles (C). The TMS-evoked response from each of these muscles is shown when stimuli were applied while the subject was contracting the quadriceps (D) and while contracting the hamstring group (E). The time of TMS is indicated by the arrows. Records are taken from a subject in group 3, who had sustained an L1 burst fracture.

subject was able to produce an EMG interference pattern during a voluntary contraction effort, even if that contraction resulted in the discharge of only one motor unit.

Response Latency

Figure 8 shows the mean (\pm standard deviation) of the minimum TMS-evoked response latencies in the 11 (for AB and group 1 SCI subjects) or five (for group 2 and group 3 SCI subjects) muscles examined (excluding data from hip adductors, for which cross-talk could not be

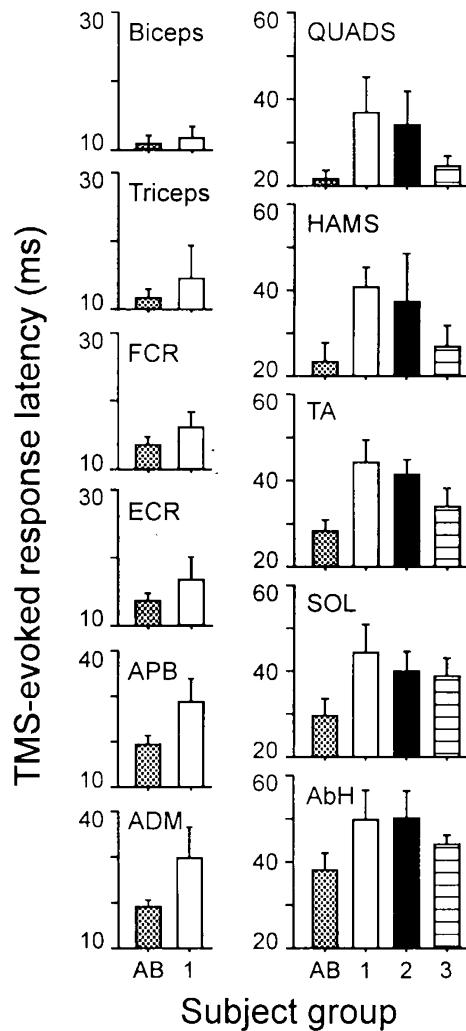


FIG. 8. Average (\pm standard deviation) minimum TMS-evoked response latency for different muscles studied of the upper limb (left) and lower limb (right). Data are included for able-bodied (AB) subjects (stippled bars), and three groups of SCI subjects, as follows: 1, cervical (open bars); 2, thoracic (T2–T10; filled bars); 3, thoracolumbar (T11–L2; striped bars). Note that the vertical axes are not identical across muscles.

TABLE 3. BETWEEN-GROUP COMPARISONS OF DIFFERENCES IN MINIMUM TMS-EVOKED LOWER LIMB MUSCLE RESPONSE LATENCIES, INCLUDING DATA FROM ABLE-BODIED SUBJECTS (AB) AND EACH OF THE THREE SUBGROUPS OF SCI SUBJECTS (GROUP 1, CERVICAL; GROUP 2, THORACIC; GROUP 3, THORACOLUMBAR)^a

	Quads	Hams	TA	Soleus	AbH
AB vs. 1	SIG	SIG	SIG	SIG	SIG
AB vs. 2	SIG	SIG	SIG	SIG	SIG
AB vs. 3	NS	NS	NS	NS	NS
1 vs. 2	NS	NS	NS	NS	NS
1 vs. 3	SIG	SIG	SIG	NS	NS
2 vs. 3	SIG	SIG	NS*	NS	NS

^aAs an example, in AB subjects, the mean response latencies of each of the lower limb muscles tested were significantly less than those for subjects in groups 1 and 2, but none were different from those measured in group 3 subjects. $p < 0.05$ for statistical significance (SIG) to Tukey post hoc testing; otherwise, differences between groups were not significant (NS).

* $p = 0.07$.

ruled out, as discussed above). In AB subjects, we correlated subject height and the minimum response latency of six muscles (biceps, FCR, APB, QUADS, TA, and AbH, chosen to reflect proximal, intermediate and distal locations in both upper and lower limbs). These relationships were significant ($p < .05$) for all but the biceps brachii muscle. However, correlations of height and response latency for group 1 and group 2 SCI subjects were not significant for any of the muscles examined. Thus, we did not correct measured latencies for height when calculating response delays of TMS-evoked responses in SCI subjects.

Given the pronounced muscle weakness in many of the target muscles examined within SCI subjects, it was not always possible to accurately distinguish between the onset of the TMS-evoked response in the averaged record and the preceding background EMG activity. In such cases, which made up fewer than 4% of our trials, we did not assign a response latency. When latencies could be established reliably, the mean latencies to TMS-evoked upper limb muscle responses in persons with cervical injuries (i.e., group 1) were significantly greater than those for AB subjects for all but the biceps muscles, based on overall ANOVA and Tukey post hoc testing. For lower limb muscles, the average TMS-evoked response latencies in persons with cervical (group 1) and thoracic (group 2) injury were all significantly greater than the latencies for comparable muscles in AB subjects. Conversely, none of the differences in averaged TMS-evoked muscle response latencies between AB and group 3 subjects (thoracolumbar SCI) were significant (Table 3 sum-

marizes these lower limb comparisons). For comparisons between different SCI groups, TMS-evoked response latencies for any given muscle were not significantly different between group 1 and group 2 subjects. However, response latencies for proximal muscles (QUADS; HAMS) in these two SCI groups were significantly longer than in group 3 subjects.

Statistical comparison of the TMS-evoked response delays in SCI subjects relative to data from AB subjects revealed a significant group effect ($p < 0.0001$), indicating that delays were not similar in the 3 groups. There was no significant difference in response delay among muscles ($p = 0.592$) and no significant interaction of muscle-by-group ($p = 0.375$, indicating that no muscles were preferentially affected in a particular group). Further testing of the group effect finding revealed significant differences in delays between group 3 versus group 1, and group 3 versus group 2 ($p < 0.0001$ for both comparisons). There was no significant difference between group 1 and group 2 delays ($p = 0.289$).

Figure 9 shows contraction strength (as gauged by EMG interference pattern) and TMS-evoked response latency for both the proximally located quadriceps (Fig. 9A) and distally located abductor hallucis (Fig. 9B) muscles from SCI subjects in groups 1 and 2. If this relationship was significant, one would expect that increased EMG recruitment (hence clinical strength) would correspond to shorter (i.e., closer to normal) TMS-evoked response latencies. However, there was no significant relationship between minimum TMS-evoked response latency and contraction strength during voluntary contractions of either the quadriceps or AbH muscles in the subjects studied.

Figure 9 also shows the average TMS-evoked latency from AB subjects for both quadriceps and AbH muscles, allowing comparison of the range of responses from SCI subjects. Note that not one single latency from any of the SCI subjects studied, regardless of subject height, was less than the average latency of the AB subjects. Moreover, the responses from SCI subjects are all skewed toward prolonged latencies, accounting for the much higher standard deviations in the means of data from SCI compared to AB subjects evident from Fig. 8.

DISCUSSION

In this study, we attempted to document the pattern of preserved volitional motor function in a large population of persons with SCI at different levels and of differing severity (motor-complete and motor-incomplete), using a combination of voluntary contractions and transcranial magnetic stimulation. This latter technique also allowed examination of the latency to evoked responses in representative muscles affected by the spinal cord injury in these individuals. Many of the muscles examined as part of this study had not been included in published studies using TMS for SCI subjects. Moreover, the great majority of subjects with SCI included for study had sustained their injury more than 9 months previously. Our goal is to now use this information for comparison to the pattern and time-course of motor recovery after acute SCI, in order to gain insight into the mechanisms underlying the restoration of axonal conduction in central motor pathways following spinal cord injury. Such studies may (1) help direct development of animal models for treat-

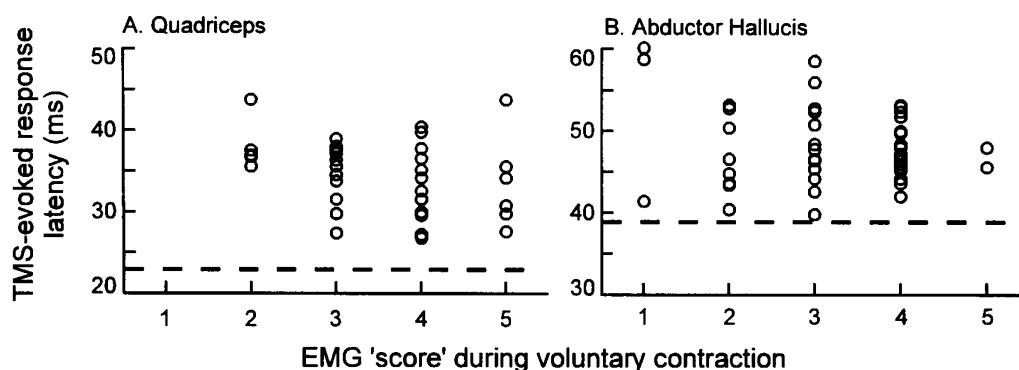


FIG. 9. Absolute TMS-evoked response latency in SCI subjects relative to EMG score during a voluntary contraction attempt. Data for the proximally-located quadriceps (A) and the distal abductor hallucis (B) muscles are shown. EMG scores of 3 and 4 often gave rise to near-identical response latencies, accounting for the considerable overlap of the open data points. There was no significant relationship in either muscle for these two variables. The dashed line on each panel shows the average TMS-evoked latency from able-bodied subjects for the quadriceps (A) and abductor hallucis (B) muscles, respectively.

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ment which are more appropriate for the human; (2) aid in selecting patients for particular (and as yet unspecified) treatments; and (3) serve as an objective measure of treatment outcome.

Threshold and Distribution

Fewer muscles were recruited by TMS in the SCI subjects examined, and stimulus intensity thresholds were higher for muscles left weakened by the injury compared to those in AB subjects. Threshold determinations were made while the subject was at rest (i.e., not making a background contraction at the time of stimulation). Because of this, approximately one-third of the motor-incomplete subjects tested did not have evoked responses to TMS in any lower limb muscles, even when using a stimulus intensity of 100% for these threshold measures. However, responses were seen in one or more target muscles when stimuli were applied while subjects were contracting that muscle at the time of stimulus (e.g., see Fig. 3). Thus the difference in TMS threshold intensities between upper and lower limb muscles for subjects with motor-incomplete SCI must be higher, on average, than indicated by the values reported here (i.e., ~63% and 78% for upper and lower limbs, respectively). In practice, we typically used 100% stimulus intensities in the SCI subjects, and always examined evoked responses while the subject was attempting a facilitating contraction in the target muscle. For these reasons, we are confident that the stimulus intensity and paradigms used were optimal for eliciting motor-evoked responses to TMS in the target muscles selected.

There was almost perfect agreement between a person's ability to voluntarily produce a visible muscle contraction (avoiding various movement-related facilitation techniques which might trigger spasms) and the presence of an evoked response to TMS in that muscle. The only exceptions were seen in four individuals who were believed to be "motor-complete" in lower limb muscles based on physical examination, but in whom motor unit recruitment in a lower limb muscle was evident via EMG recordings (AbH in three subjects; AbH and TA in one subject). In these few cases, then, the term "motor-complete" was not an accurate reflection of the neurologic status of these subjects. Thus, EMG recordings from a muscle can be a more sensitive indicator of preserved voluntary innervation than visible contractions alone. Such cases were rare in the present study, however, and the amount of EMG produced by maximal voluntary effort in these cases was of no functional consequence. These findings argue against the routine use of EMG measures in place of the more traditional "manual muscle test" for the clinical assessment of motor function in

persons with central motor disorders, or the use of TMS as a predictor of outcome in persons who are motor-complete during the acute period after SCI (Macdonell and Donnan, 1995). For our purposes, the particular value of EMG measures comes when combined with TMS, allowing repeated studies of parameters such as threshold intensity and response latency.

For upper limb muscles, the distribution of TMS-evoked responses in motor-incomplete individuals was, in most cases, consistent with the level of injury and the relative origin of motoneurons to the different target muscles. For example, the ADM muscle, which receives its innervation from the most caudal portion of the cervical enlargement, had the lowest probability of responding to TMS in the population studied. The high probability of observing TMS-evoked responses in the triceps brachii muscle in cervical SCI motor-complete subjects examined in this study was of some surprise, given that the majority of this muscle's innervation arises from C7 (Ferner and Staebesand, 1983; Kendall and McCreary, 1983), although some sources indicate a contribution to this muscle from the C6 level (Kendall and McCreary, 1983).

For the lower limb, a key observation in the present study was that persons with motor-incomplete lesions to the cervical or thoracic spine (at or rostral to T10) had more widespread preservation of motor function and TMS-evoked responses in their distal lower limb muscles compared to more proximal (i.e., thigh) muscles. This was particularly evident in the AbH muscle, an intrinsic muscle which mediates plantar-flexion of the great toe. As indicated in Fig. 6, there were no single exceptions to this observation. In contrast, persons with injuries caudal to the T10 level were more likely to have motor preservation in the proximal lower limb musculature compared to more distal muscles.

These findings appear to contradict findings from a recent study of persons with neurologically incomplete injury to the cervical spinal cord (Graziani et al., 1995), where it was concluded that the hip adductors had a higher probability of recovery than muscles controlling toe movements. In the study by Graziani et al. (1995), subject enrollment was restricted to persons with either the central cord or Brown-Sequard syndromes, whereas the present study excluded individuals with central cord syndrome, and did not encounter persons with the Brown-Sequard syndrome. Moreover, limb movement was the sole parameter studied, and it is unclear whether or not intrinsic muscles of the foot were examined (Graziani et al., 1995).

Preservation of volitional control in proximal musculature in persons with injury caudal to T10 may simply reflect root sparing, since such injuries may include vary-

ing amounts of spinal cord and cauda equina. For example, it is not uncommon for a person with an L1 burst fracture to recover volitional hip flexion (L1 and L2 nerve roots) in the absence of ankle plantar flexion. However, root sparing cannot readily account for the distinct differences observed in the probability of TMS-evoked responses in the hamstring compared to the TA and AbH muscle of group 3 subjects. As summarized in Kendall and McCreary (1983), the TA is innervated largely by the L4 level with limited L5 input, AbH is innervated by the L4, L5, and S1 segments (without a dominant level), and the hamstring group is innervated by the L5 through S2 segments, with the S1 segment predominating (Kimura, 1989; Daniels and Worthingham, 1980). Thus the hamstring is a muscle group that, by several reports, receives its innervation from a site relatively caudal within the spinal cord, yet in group 3 subjects is much more likely to respond to TMS than either the TA or AbH muscles. Based on samples obtained through the studies of Bunge et al. (1997), we are currently examining the histological consequences of fractures caudal to T10, to determine whether there may be differential involvement of lateral compared to ventral motor tracts, as recently reported in a small sample (Bunge et al., 1997), which might lead to preferential sparing of innervation to proximal musculature of the lower limb, for reasons described below.

The lateral motor tracts (corticospinal and rubrospinal) and ventral motor tracts (reticulospinal and vestibulospinal) of the spinal cord are known to innervate motoneuron pools of lower limb muscles in a target-specific manner. (Although good evidence exists in the monkey that the rubrospinal tract is functionally similar in some respects to the corticospinal tract (Mewes and Cheney, 1991), evidence for the former pathway in humans remains scarce (Schoenen and Grant, 1990), and further discussion of lateral tract action will be confined to the corticospinal tract.) Based on primate studies, the lateral corticospinal tract has a greater density of direct, monosynaptic projections to motoneurons of distal lower limb muscles—particularly intrinsic muscles of the foot—than to more proximal lower limb muscles (Jankowska et al., 1975). In contrast, motoneurons innervating muscles of the trunk and proximal lower limb have been reported to receive input predominantly from the medial reticulospinal and vestibulospinal tracts (Kuypers, 1981), with other inputs including fibers in the uncrossed (anterior) corticospinal tract (Nathan et al., 1990), and long descending propriospinal fibers (Nathan, 1994).

The very high prevalence of TMS-evoked responses in distal lower limb muscles, particularly the AbH muscle of the foot, in persons with motor-incomplete SCI to the cervical or thoracic spine is likely due to functional

sparing of axons in the lateral corticospinal tracts. By simple probability, those muscles whose motoneurons receive the highest proportion of corticomotoneuronal innervation (i.e. intrinsic muscles of the foot and other distal muscles) would be most likely to respond to TMS once conduction is restored in some minimum number of lateral corticospinal tract axons. Conversely, TMS-evoked activity in proximal lower limb muscle groups, including quadriceps or hamstring, would be less probable, since fewer corticospinal axons innervate these target populations of motoneurons. Moreover, movement studies following selective spinal cord lesions suggest that the role of the ventral motor tracts in the generation of isolated (or “fractionated”) lower limb movements in humans is limited (Nathan, 1994). In order for this argument to be valid, there must be no somatotopic organization of lateral corticospinal tract fibers in the spinal cord. Despite historical references to the contrary (e.g., Ferner and Staubesand, 1983), recent studies argue against somatotopic “layering” of corticospinal fibers in the spinal cord (Schoenen and Grant, 1990; Levi et al., 1996), consistent with our hypothesis.

Latency

The TMS-evoked minimum response latencies we observed in the AB subject population are within the range of published values for the APB (Macdonell et al., 1989; Eisen and Shtybel, 1990; Hufnagel et al., 1990; Machida et al., 1991; Segura et al., 1992) and the TA muscles (Masur et al., 1989; Eisen and Shtybel, 1990; Booth et al., 1991; Brouwer and Ashby, 1992; Furby et al., 1992; Segura et al., 1992). Comparisons of latencies for the remaining nine muscles that we examined in this study to findings from other studies are difficult due to a paucity of published results. In this study, all TMS-evoked latencies in AB subjects were significantly correlated with height, with the exception of biceps brachii.

We did not measure central motor conduction time for the upper and lower limb muscles studied; to have done so would have required either cervical and/or lumbar spinal nerve root stimulation (Ugawa et al., 1989; Eisen and Shtybel, 1990), or needle electrode recordings and motor nerve stimulation. For the former approach, many of the subjects with SCI examined in this study had implanted spinal instrumentation to aid fusion of surgically-managed spine fractures; the use of nerve root stimulation for central motor conduction estimates would be ill-advised in such subjects. For central motor conduction measures based on M- and F-wave determinations, the large number of muscles examined with TMS in the present series would have lengthened the protocol by a considerable period of time. Nevertheless, our exclusive

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reliance on absolute TMS-evoked response latencies as an indicator of central motor conduction represents a clear weakness in the study design, as we do not correct for subject height, and we must assume that there is no significant peripheral neuropathy (which might prolong conduction latencies independent of central motor conduction abnormalities). Nerve root involvement as a consequence of spinal cord injury is common, but typically involves roots within several levels of the epicenter of the lesion (Peckham et al., 1976; Berman et al., 1996). Since many of our studies included lower limb muscles in subjects with cervical injury, the probability of abnormal peripheral nerve conduction in lower limbs of such subjects is likely to be remote. Finally, previous studies of subjects with SCI show normal or near-normal peripheral conduction velocities and segmental reflex latencies (Brouwer et al., 1992; Calancie et al., 1993), suggesting that slowing of peripheral motor conduction can account for only a minor component of the conduction delays seen in the present study. For these reasons, and in agreement with Eisen (1994), we believe it is appropriate to use serial measures of minimum TMS-evoked muscle response latency to determine whether central motor conduction improves over time in parallel with clinical improvement in muscle function.

In subjects with SCI, evoked response latencies to muscles in either upper (for quadriplegics) or lower limbs (for quadri- or paraplegics) were, on average, delayed by significant amounts from those values seen in AB subjects, with the exception of proximal lower limb muscles in group 3 subjects, as discussed below. The extent of that delay was less pronounced for the triceps and wrist flexors/extensors, whereas intrinsic hand muscles demonstrated average prolongations in latency that rivaled those of lower limb muscles studied in group 1 SCI subjects. For example, the delay in averaged TMS-evoked latencies in the ADM muscle for group 1 SCI subjects—10.5 msec—was comparable to averaged delays in the abductor hallucis muscles (10.5 msec) in this subject population. Similar delays were seen for lower limb muscles in group 2 SCI subjects compared to subjects in group 1, such that results from these two populations were not significantly different. In other words, the delays in TMS-evoked response latency were similarly prolonged for all lower limb muscles studies in group 1 and group 2 subjects, but were shorter in group 3 subjects.

TMS-evoked response latencies were not significantly different between AB and group 3 SCI subjects for any of the lower limb muscles examined. Since absolute differences between these two groups in mean evoked response latencies were as much as 7.3 msec (soleus), this absence of statistical significance probably reflects in part the relatively small sample size in the group 3 popula-

tion. However, the absolute TMS-evoked response latencies for proximally located lower limb muscles were very similar between AB and group 3 subjects (differences in mean values of 1.5 and 3.1 msec for quadriceps and hamstring muscle groups, respectively). This similarity in latency suggests that the nerve roots innervating these proximal muscles were either caudal to the primary neurologic level of lesion, and/or the central motor tracts mediating TMS-evoked responses for quadriceps and hamstring groups were less prone to damage as a result of the injury. Thus in agreement with distribution findings, the hamstring muscle in group 3 subjects shows greater similarity to the quadriceps (i.e., proximal) muscle with respect to TMS-evoked response latency than to more distal muscles in the lower limb, despite the relatively distal source of motoneuron innervation for the hamstring (i.e., L4 through S2; Kendall and McCreary, 1983).

The similarity in TMS-evoked latency of muscles whose motoneurons lie at widely different levels of the spinal cord suggests that the conduction delay due to the lesion is restricted to a focal zone of injury and does not extend caudally within the descending motor pathways mediating TMS-evoked responses in lower limb muscles (Brouwer et al., 1992). Otherwise, one would expect that with the much longer central conduction pathway for motor tracts which innervate lower limb motoneuron pools, widespread slowing of central conduction velocity would cause much more pronounced delays in TMS-evoked response latencies of these muscles—particularly for those innervated from the most caudal portions of the lumbar enlargement—than were observed in the present study. Increased dispersion between I-waves as they traverse the lesion can also be ruled out for the same reason. Similar conclusions about the lesion associated with spinal cord injury typically being focal in nature were reached by Bunge et al. (1993) through detailed histopathological examination of spinal cords, which had been obtained postmortem from persons who had sustained traumatic SCI (and see Becerra et al., 1995; Hayes and Kakulas, 1997). Physiologic studies to corroborate these anatomic findings are necessary because in most cases, the ability to resolve histopathology of human postmortem samples is limited by suboptimal fixation of the tissue relative to animal models (i.e., transcardiac perfusion is not possible in humans). Given this limitation, modest alterations in axon pathology at sites distant to the epicenter of spinal trauma might not be apparent histologically, yet could have a significant impact on axonal conduction properties.

The extent of delay in TMS-evoked responses is consistent with focal conduction showing due to myelin loss at the lesion's epicenter, based on our preliminary stud-

ies of magnetic resonance images from some of the subjects included in this study (Calancie, in preparation). Evidence for myelin loss at the epicenter of a traumatic injury to the spinal cord in animal studies continues to accumulate (Blight and Young, 1989; Waxman, 1989; Hayes, 1994). This was recently confirmed in human tissue following traumatic SCI (Becerra et al., 1995; Alexeeva et al., 1997). Recent studies show individual axons which have been demyelinated are capable of conducting action potentials across the lesion (Felts et al., 1997). Although consistent with myelin loss, our findings of delayed TMS-evoked responses in the present study do not indicate whether the conduction abnormality affects all fibers equally in the descending tracts mediating the evoked response, or whether a subset of fibers have normal conduction velocities, but are incapable through their action alone of bringing spinal motoneurons to threshold. We addressed this in a recent study using a conditioning-test paradigm with combination of segmental (i.e., H-reflex) and central (i.e., transcranial magnetic stimulation) excitatory inputs to the soleus motoneuron pool in a subset of subjects included in the present study. Unlike able-bodied subjects, we were unable to demonstrate any short-latency effect of TMS on segmental excitability in persons with motor-incomplete cervical SCI, suggesting a widespread slowing of conduction in all fibers mediating the TMS-evoked motor response in soleus (Alexeeva et al., 1998; Rothwell et al., 1984; Wolfe et al., 1996).

To relate the contraction strength (as judged by EMG interference pattern) with TMS-evoked response latency, the QUADS and AbH muscles were chosen for analysis because each had a large sample size associated with it, and they represented a proximal (i.e., significant extrapyramidal innervation) and distal (i.e., significant pyramidal innervation) muscle. There was no obvious relationship between the magnitude of contraction and the latency of TMS-evoked responses for either of these muscles (Fig. 9). A similar conclusion was reached for the tibialis anterior muscle in SCI subjects by Brouwer et al. (1992). In other words, weak muscles did not tend to have longer latency responses to TMS than clinically stronger muscles. Instead, there was a wide range of minimum evoked response latencies to TMS for muscles with very different levels of volitional recruitment (hence strength). It remains to be determined whether, at the earliest point after injury, any improvement in TMS-evoked response latency can be detected with the present methodology. Such information might further our understanding of the physiologic basis for functional improvement in muscle strength after spinal cord injury in humans.

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