A Comparison Of Descending Evoked Potentials And Muscle Responses After Transcranial Magnetic Stimulation And Skull Base Electrical Stimulation In Awake Human Subjects

by

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A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy,
Graduate Department of the Institute of Medical Science,
University of Toronto.

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David Allen Houlden, Institute of Medical Science, University of Toronto. PhD thesis, 1997.

Thesis Abstract

Transcranial magnetic stimulation (TCMS) and electrical stimulation over the skull base (SBS) can evoke muscle responses from the arms and legs. TCMS excites corticospinal neurons that send volleys down the corticospinal tract to preferentially activate small hand muscles. The motor pathways activated after SBS are not clearly understood but our preliminary studies demonstrated that SBS preferentially activated triceps (a muscle with that receives weak corticospinal excitation) and not small hand muscles which suggested SBS activated spinal motoneurons differently than TCMS.

On the basis of these findings, the characteristics of the descending spinal cord evoked potentials (SCEPs) after TCMS (leg area) and SBS were compared to determine if the different pattern of muscle activation was related to differences in SCEPs. For the first time, recordings were obtained from awake, neurologically intact human subjects with dorsal column stimulators (DCS) epidurally positioned at Th8. The DCS electrode was temporarily used as a recording electrode during the experiments. The SCEP after TCMS had more waves and a longer duration

than that after SBS but both had fast conduction velocities. Anaesthesia diminished the later SCEP waves after TCMS but had little effect on the first wave or the SCEP after SBS. It was concluded that TCMS directly and indirectly excited corticospinal neurons and the pattern of muscle activation was likely dependent on the area of cortical representation for a given muscle, the orientation and excitability of corticospinal neurons in that area and the excitability of the spinal motoneurons. In contrast, SBS activated long tracts so muscle activation was dependent on spinal mechanisms alone.

To determine the role of cortical excitability in the facilitation of muscle responses, SCEPs were recorded during rest and voluntary activation of tibialis anterior (TA). Increased excitability of corticospinal neurons during voluntary activation of TA (indicated by increased SCEP rectified area) was observed at threshold (T) TCMS intensities but not above T. This suggested muscle facilitation was related to increased excitability in some corticospinal neurons (that was only detected at T) as well as increased excitability in spinal motoneurons.

Acknowledgements

I would like to thank all of the normal subjects and patients who volunteered to participate in these experiments, Dr. Mahmood Fazl and Dr. Graham Vanderlinden for referring the patients to me, and to the Medtronic company for loaning me a DCS electrode. I would also like to thank the people who assisted me in the artwork, graphs, statistical analysis and literature search. In this regard I would like to acknowledge the contribution of Patsy Cunningham, Ming Wei Li, Marko Katic and Ken Klettke.

I would like to acknowledge the support of the Acute Spinal Cord Injury Program at Sunnybrook Health Science Centre and, in particular, Dr. David Rowed for being a constant source of support and guidance throughout my career at Sunnybrook.

I would also like to thank the members of my Thesis Committee; Drs. Bill MacKay, Peter Ashby and Charles Tator for their constructive criticism and enduring support during all phases of the research. I would like to especially thank Dr. Michael Schwartz who, with his inquisitive manner, nudged me on to the next level of investigation and achievement. For the many hours of discussion and guidance he gave to me, I am grateful.

I would like to extend thanks to my parents, Donald and Margaret Houlden, for valuing education and encouraging me in my academic pursuits. Finally, I would like to thank my wife Patty, for her moral support and for carrying the extra family responsibilities during the preparation of this thesis.

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Terms and Abbreviations

Bi	Biceps
C	Cervical vertebrae
CCT	Central conduction time
CEP	Cerebellar evoked potential
cm	Centimetre
CMAP	Compound muscle action potential
CNS	Central nervous system
Cz	Vertex scalp position
D wave	A descending volley measured from the spinal cord after direct activation of corticospinal neuron
DCS	Dorsal column stimulating electrode
DTR	Deep tendon reflex
EEG	Electroencephalography
EMG	Electromyogram
EPSP	Excitatory postsynaptic potential
F response	A late EMG signal after antidromic activation of spinal motoneurons by supramaximal electrical stimulation of motor axons
FDI	First dorsal interosseous muscle
G1	Grid one of a differential amplifier
G2	Grid two of a differential amplifier
H reflex	Hoffman reflex. A monosynaptic reflex after stimulation of Ia sensory fibres within a peripheral nerve that results in a late EMG response.
Hz	Hertz
I wave	A descending volley measured from the spinal cord after indirect activation of corticospinal neuron
IPSP	Inhibitory postsynaptic potential
kHz	Kilo Hertz (10^3 Hz)
kOhm	Kilo Ohm (10^3 Ohms)
L	Lumbar
m/sec	Meters per second
M wave	The direct muscle response after stimulation of its motor nerve
mg	Milligram (10^{-3} grams)
MEP	Motor evoked potential
MRC	Medical Research Council muscle grading system
ms	Millisecond (10^{-3} seconds)
Mv	Millivolt (10^{-3} Volts)
μV	Microvolt (10^{-6} Volts)
N_2O	Nitrous oxide
O_2	Oxygen
PCT	Peripheral conduction time

PSTH	Peristimulus time histogram
Quad	Quadriceps muscle
SBS	Percutaneous electrical stimulation at the skull base
SCEP	Spinal cord evoked potential
SCM	Sternocleidomastoid muscle
SD	Standard deviation
SE	Standard error of the mean
Sol	Soleus muscle
T	Threshold. The lowest stimulus intensity required to evoke a response.
TA	Tibialis anterior muscle
TCES	Transcranial electrical stimulation
TCMS	Transcranial magnetic stimulation
Th	Thoracic vertebrae
V	Volt

CHAPTER I

Introduction

In the last fifteen years, new techniques for electrophysiological assessment of central motor pathways have improved our understanding of the function of central motor pathways in health and disease. Transcranial magnetic stimulation (TCMS) and transcranial electrical stimulation (TCES) have become accepted ways of activating the corticospinal pathways. Nevertheless, there is a lack of knowledge about the way these techniques activate corticospinal neurons and this makes interpretation of the results difficult.

Merton and Morton (1980) demonstrated that electrical stimulation over the human scalp (TCES) resulted in muscle contractions contralateral to the side of stimulation. TCES directly activated corticospinal neurons and/or their axons within the brain that made monosynaptic projections to motoneurons in the spinal cord (Zidar et al., 1987; Day et al., 1989). Spinal cord recordings (SCEPs) after TCES or anodal stimulation of the brain surface have been studied in anaesthetized animals (Patton and Amassian, 1954; Kernell and Wu, 1967; Edgeley et al., 1990; Amassian et al., 1990) and humans (Thompson et al., 1991). The descending spinal cord evoked potential (SCEP) had multiple peaks with the earliest peak (D wave) corresponding to direct activation of pyramidal cells and the subsequent peaks (I waves) reflecting indirect activation of pyramidal cells via cortico-cortical connections. Muscles used in fine motor control were more readily activated after stimulation of the motor cortex than

other muscles.

In 1985, Barker demonstrated that transcranial magnetic stimulation (TCMS) could also produce muscle responses (Barker et al., 1985a; Barker et al., 1985b). The brain was stimulated by a magnetic field induced by a rapidly changing high voltage that passed through a coil. TCMS was not painful (unlike TCES) because the electromagnetic field induced electrical currents in the brain without causing the high current densities at the scalp that result in pain. This was possible because biological tissue is permeable to magnetic fields (Ward, 1986). The result was painless activation of cortical neurons. Consequently, TCMS has been widely used as a means of non-invasively activating the corticospinal system in normal subjects and patients with neurological disorders.

Studies comparing the latency of muscle responses following TCES and TCMS have shown that evoked muscle responses following TCES have shorter latencies than those following TCMS. Some investigators believe that TCES directly activates pyramidal cells while TCMS indirectly activates pyramidal cells so the time necessary for indirect activation of pyramidal cells accounts for the longer latency after TCMS. The relationship between the D and I waves recorded directly from the spinal cord and the muscle responses after TCMS or TCES has not previously been investigated in awake human subjects.

Ugawa demonstrated that high intensity percutaneous electrical stimulation at the skull base (SBS) resulted in contraction of limb muscles bilaterally (Ugawa et al., 1991b). They attributed the muscle contractions to activation of the corticospinal tract at the cervico-medullary junction. This conclusion was based on collision studies between cortical and brainstem volleys (Ugawa et al., 1991b) and from patients with supratentorial lesions with, "clinical pyramidal signs", who had abnormally high SBS thresholds (Ugawa et al., 1992). In these experiments, they recorded from muscles known to receive strong corticospinal excitation (Clough, 1968; Alstermark and Sasaki, 1985).

The order of activation in muscles known to receive either strong or weak excitation from the corticospinal pathway has not been studied in normal subjects or patients with neurological disorders. The characteristics of the descending SCEP recorded directly from the spinal cord after SBS has not been investigated in awake human subjects.

A high voltage square wave stimulus pulse grossly applied to the base of the skull may activate many descending pathways that affect alpha motoneuron excitability (Fig. 1). These pathways are described below.

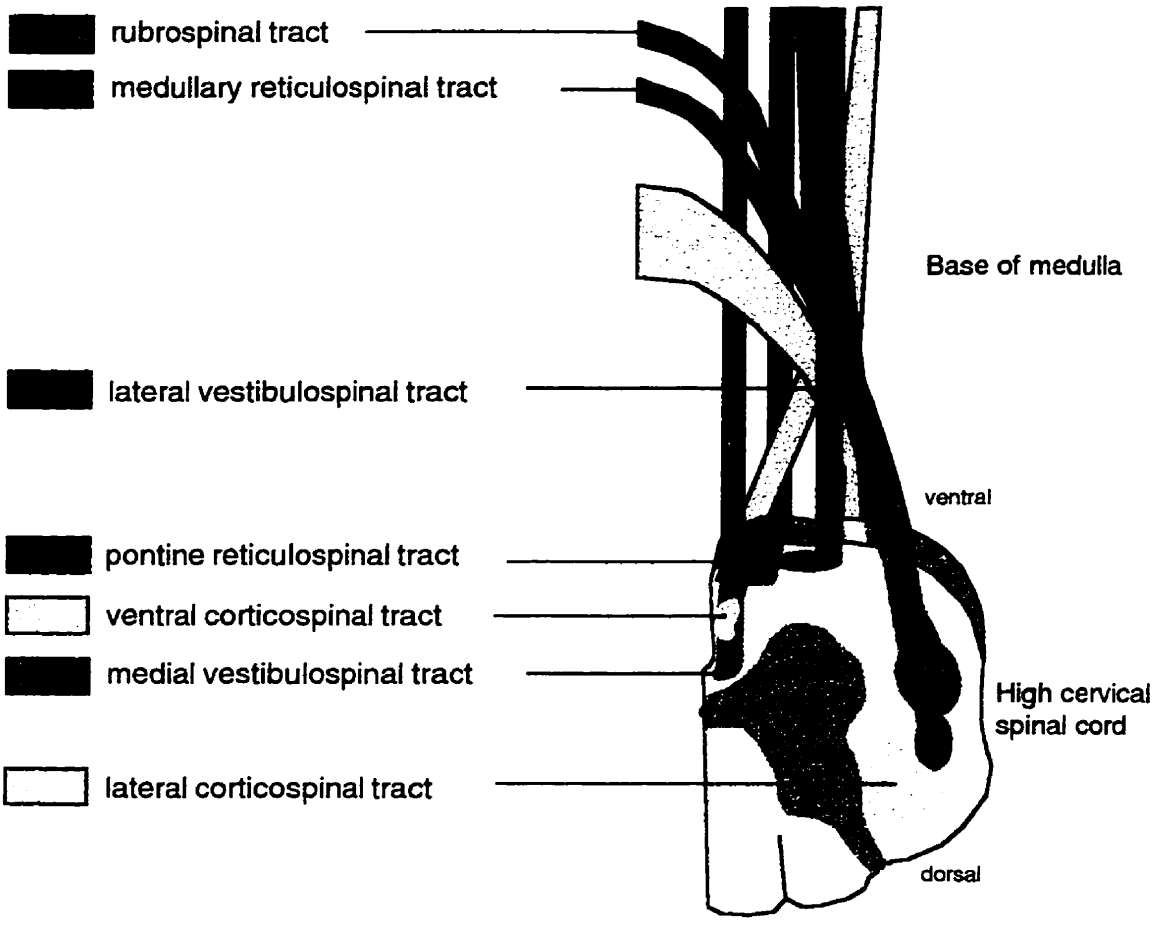


Figure 1. A schematic representation of the major descending motor pathways at the base of the medulla and high cervical spinal cord that may be activated by percutaneous electrical stimulation at the skull base. The rubrospinal tract, part of the medullary reticulospinal tract and most of the lateral corticospinal tract are crossed pathways. The location of the reticulospinal and vestibulospinal tracts in the high cervical spinal cord were taken from Nathan et al., 1996.

The Corticospinal Pathways

The corticospinal pathways originate from pyramidal cells in the sensorimotor cortex that send axons down the whole length of the spinal cord to make mono- and polysynaptic connections with spinal motoneurons but some corticospinal fibres project to the cells of origin for other (non-corticospinal) motor pathways (ie. rubrospinal and reticulospinal) located in the brainstem that send their own projections down the spinal cord. Other fibres from the sensorimotor cortex project to the cerebellum, which in turn, influences the cells of origin for all descending motor pathways.

The largest pyramidal cells in the motor cortex (Betz cells) are located in layer V and receive excitatory and inhibitory intrinsic input from basket and stellate cells as well as excitatory or inhibitory extrinsic input from the premotor cortex, primary sensory cortex and thalamus (Amassian, 1987b). The pyramidal cells are also capable of recurrent inhibition through interneurons located in layer V. Most corticospinal fibres decussate in the pyramids of the medulla and descend contralaterally in the lateral corticospinal pathway located in the dorsolateral funiculus of the spinal cord, but a small group remain ipsilateral and descend in the ventral corticospinal tract located in the ventral funiculus. More corticospinal fibres project to motoneurons in the cervical enlargement than the lumbar enlargement likely because there are a greater number of cortical

colonies that project to the arm and hand than the leg and foot (Bernhard and Bohm, 1954). Corticospinal fibres enter the spinal grey in the intermediate zone and terminate in laminae V - IX. Only a small proportion of corticospinal fibres form monosynaptic connections in the spinal cord. Most of the spinal terminations of the motor cortex are in the intermediate zone where they may synapse onto spinal interneurons. A single corticospinal neuron can send projections to more than one alpha motoneuron (Fetz and Cheney, 1978) and a single motoneuron can receive input from more than one corticospinal neuron (Jankowska et al., 1975). Nevertheless, muscle movements after direct stimulation of the sensorimotor cortex are very discrete (ie. movements in single digits can be elicited) and highly dependent on stimulus location suggesting a highly focused somatotopic system (Kuypers and Huisman, 1982).

The densest corticospinal projections to motoneurons come from the lateral corticospinal tract whose fibers terminate in the ventral horn on cells that supply the most distal muscles of the limb. Fewer corticospinal projections come from the ventral corticospinal tract whose fibres terminate in the ventromedial spinal grey on cells that supply axial muscles. Electrical stimulation of cortical colonies in the baboon motor cortex caused monosynaptic excitatory action on motoneurons of distal muscle groups (median nerve and ulnar nerve innervated muscles) more than proximal muscle groups (biceps and triceps) (Phillips and

Porter, 1964). Furthermore, stimulation resulted in early inhibition in approximately half of the triceps motoneurons tested. Studies using transcranial magnetic or transcranial electric stimulation in awake humans verified that motoneurons supplying small hand muscles and wrist flexors contralateral to stimulation were activated at lower stimulus intensities and to a larger extent than those supplying triceps and biceps (Rothwell et al., 1987; Brouwer and Ashby, 1990).

The primary sensory cortex sends projections down corticospinal pathways and direct stimulation of the primary sensory cortex can produce movements. Consequently, the term sensorimotor cortex is used when referring to the area of brain involving the pre- and post-central gyri. The projections from the primary sensory cortex terminate further away from alpha motoneurons (laminae IV, V, VI) than projections from the primary motor cortex (laminae IV - IX) (Brodal, 1981). However, ablation of primary motor cortex in monkeys obliterated descending SCEPs after stimulation of primary sensory cortex suggesting they were contingent on the primary motor cortex through cortico-cortical connections (Patton and Amassian, 1960). The pyramidal projection from sensory areas to spinal cord is probably used in modulation of sensory input to the brain rather than muscle activation (Rothwell, 1994a).

Lesioning studies in monkeys have shown that a considerable amount of motor control is regained during the postoperative recovery period after bilateral transection of the pyramidal tracts (corticospinal tracts) but the capacity to execute individual finger movements is permanently abolished (Lawrence and Kuypers, 1968 a, b). The motor control that was regained in the recovery period was attributed to preservation of descending brainstem pathways.

The Brainstem-Spinal Pathways

The reticulospinal, vestibulospinal, tectospinal and interstitiospinal pathways have been classed as medial brainstem pathways while the rubrospinal pathway has been classed as a lateral brainstem pathway. The coeruleospinal, sub-coeruleospinal and raphespinal pathways have been classed as bulbospinal pathways.

The Reticulospinal Pathways ("medial" brainstem pathway): The reticulospinal pathway originates from cells loosely grouped together in nuclei within the pons and medulla with some nuclei located as rostral as the mesencephalon and diencephalon. The nuclei located in the pons send ipsilateral projections down the medial reticulospinal pathway located in the ventral funiculus to enter the medial part of the intermediate zone and terminate on neurons in lamina VIII and VII along the whole length of the spinal cord but proportionally fewer fibres

descend to the lumbosacral spinal cord than the cervical spinal cord in humans (Nathan et al., 1996). The nuclei located in the medulla send ipsi- and contralateral projections down the lateral reticulospinal tract located mainly in the lateral funiculus to terminate on neurons in laminae VII, VIII, IX with some making monosynaptic connections to alpha motoneurons. Many of the neurons in the spinal grey that receive projections from the reticulospinal pathways send projections back into the spinal white matter to form propriospinal pathways thereby creating a diffuse spinal system with a high degree of collateralization. The reticular nuclei also send projections to the motor cortex through the thalamus and receive input from the vestibular nuclei, cerebellum, sensorimotor cortex and spinal cord. In general, the pontine reticulospinal pathway is thought to be involved in the pre-motor organization of voluntary and reflexive synergistic muscle contractions while the medullary reticulospinal pathway is involved in the control of axial motoneurons. Stimulation of the reticulospinal pathway causes excitation and inhibition of axial and proximal flexor and extensor muscles in cats. Lesioning studies in monkeys have demonstrated that the reticulospinal pathways are not involved in the performance of fractionated movements involving the wrist and fingers (Lawrence and Kuypers, 1968a, b).

The Vestibulospinal Pathways ("medial" brainstem pathway): The

vestibulospinal pathways originate in cells in the medial and lateral (Deiter's) vestibular nuclei which send axons down medial and lateral vestibulospinal pathways respectively. Both descend ipsilaterally in the ventral funiculus of the spinal cord with the medial pathway positioned more medially and projecting only to cervical spinal cord levels to make monosynaptic connections with motoneurons supplying neck muscles. In contrast, the lateral vestibulospinal pathway is thought to project down the whole length of the spinal cord and enter the spinal grey through the medial part of the intermediate zone to terminate on neurons within laminae VII, VIII and IX with some making monosynaptic connections to alpha motoneurons. Few vestibulospinal fibres could be traced the L3 spinal cord in humans (Nathan et al., 1996). Stimulation of the lateral vestibulospinal pathway excites extensor muscles (Young et al., 1980; Willis and Grossman, 1981). The vestibular nuclei receive central input from the cerebellum and spinovestibular tract.

The Tectospinal and Interstitiospinal Pathways ("medial" brainstem pathways): The tectospinal pathway arises from the superior colliculus and then decussates to descend in the contralateral ventral funiculus and terminates in the upper four cervical segments (laminae VI, VII, VIII) to activate neck motoneurons (Altman and Carpenter, 1961). There is also a small bundle of interstitiospinal fibres arising from the nucleus of Cajal that receive input from the superior

colliculus (Altman and Carpenter, 1961) and descend bilaterally to the sacral level in the ventral funiculus to terminate on laminae VII and VIII in close proximity to terminal projections of the vestibulospinal tract in the cat (Nyberg-Hansen, 1966). Accordingly, it is thought the interstitiospinal pathway and vestibulospinal pathways activate similar muscles (extensors).

The Rubrospinal Pathway ("lateral" brainstem pathway): The rubrospinal pathway originates from cells in the red nucleus in the midbrain. The pathway immediately decussates and descends in the lateral funiculus in the cervical spinal cord and enters the lateral part of the intermediate zone of the spinal grey matter to terminate on neurons in lamina IV, V and VI. It is a small, highly focused system that parallels, in function, the corticospinal tract but does not extend beyond the cervical spinal cord in man (Nathan et al., 1996). Lesions of lateral brainstem pathways in monkeys caused a permanent loss of fractionated finger movements but the hand could be open and closed only as a part of muscle synergy involving an extension and flexion movement of the whole arm (Lawrence and Kuypers, 1968a, b). It receives input from the motor cortex, cerebellum and possibly indirect input from the basal ganglia (Willis and Grossman, 1981).

Coeruleospinal, Sub-Coeruleospinal and Raphespinal Pathways ("bulbospinal"

pathways): The fibres from the nucleus coeruleus, sub-coeruleus and medullary raphe nuclei descend ipsilaterally in coeruleospinal (ventrolateral funiculus) and raphespinal pathways (dorsolateral, ventrolateral and ventral funiculi) the whole length of the spinal cord in cats. The coeruleospinal and sub-coeruleospinal pathways terminate on laminae IV - IX of the spinal grey (Nygren and Olsen, 1977a). The raphespinal pathways enter the intermediate zone of the spinal grey matter and terminate on laminae I, II and V (Basbaum et al., 1976) and laminae VII, VIII and IX in monkeys (Kuypers, 1981). They make direct motoneuronal connections in the monkey but, like reticulospinal pathways that also have direct motoneuronal projections (including some to muscles of the distal extremity), they are not involved in the execution of highly fractionated movements (Lawrence and Kuypers, 1968a). These pathways may be under limbic control since the nucleus subcoeruleus receives many descending fibres from the amygdala and the nucleus subcoeruleus and the lower brainstem raphe nuclei receive descending afferents from the mesencephalic central grey and the lateral hypothalamus. These pathways have been described as a descending bulbospinal gain setting system (separate from the lateral brainstem and medial brainstem pathways) that might be instrumental in providing motivational drive in the execution of movements (Kuypers and Huisman, 1982).

Other Descending Brainstem-Spinal Pathways:

The Dorsal Columns: The dorsal column nuclei (cuneate and gracile) send projections down the length of the spinal cord through the dorsal columns to make connections with neurons in the posterior horn of the spinal grey that, in turn, form the ascending spinothalamic, spinocervical and cervicothalamic pathways (Burton and Loewy, 1977). The descending dorsal column projections are likely involved in the spinal modulation of pain (the reticulospinal and raphe spinal pathways are also involved in pain modulation) but are not likely involved in the activation of alpha motoneurons. For example, animal studies have demonstrated that dorsal column transection did not affect motor responses from the limbs after widespread spinal cord stimulation in hogs but ventrolateral spinal cord transection (primary motor tract) in hogs and ventral root rhizotomy in humans obliterated the motor responses recorded from the limbs after spinal cord stimulation (Owen et al., 1989). On awakening from anaesthesia, the animals that received the motor tract transection and the humans who received the ventral root rhizotomy demonstrated flaccid paralysis as intended. The motor responses were only mildly decreased in amplitude after dorsal root rhizotomy in anaesthetized humans.

Propriospinal Pathways:

Propriospinal cells in laminae VII and VIII send axons into the ventrolateral

funiculus to terminate on cells in other spinal segments. The propriospinal cells receive monosynaptic excitation from the corticospinal pathways and weaker excitation from the rubrospinal, reticulospinal and tectospinal pathways (Rothwell, 1994a). The propriospinal cells also receive inhibition from local interneurons that are influenced by supraspinal and peripheral sources (Hultborn and Illert, 1991). The propriospinal axons can be short (one or two spinal cord segments in length) or long (traverse the whole length of the spinal cord) and most project to many alpha motoneurons that supply muscles acting about different joints. Accordingly, it is thought that the propriospinal system is involved in the control of muscle synergies.

In summary, the reticulospinal and vestibulospinal pathways originate from nuclei in the brainstem whose projections descend in ventral spinal cord pathways to make connections with spinal motoneurons involved in body and integrated limb-body movements such as orienting movements and synergistic movements of a whole limb (not fractionated movements about the wrist and fingers). They likely interact with the propriospinal pathways and central pattern generators in the spinal cord. It has also been suggested that these brainstem motor pathways, in addition to the coeruleospinal and raphespinal pathways (through their putative neurotransmitters serotonin (raphe), noradrenaline (coeruleus), enkephalin, substance P), act as gain setting systems (McCall and

Aghajanian, 1979) which determine the overall responsiveness of the motoneurons and probably also of the interneurons, both of which represent key elements in motor control. This is supported by the fact that, in monkey, bilateral transection of the ventral and ventrolateral funiculi in the high thoracic spinal cord, which contain these pathways, abolished the responses of lumbosacral motoneurons to stimulation of the contralateral precentral cortex despite an intact lateral corticospinal tract that conducted descending SCEPs after motor cortex stimulation (Bernhard, 1955). These pathways may be especially active during circumstances that require a high level of motor activity like fight or flight response. The rubrospinal tract also originates in brainstem nuclei but has less collateralization than reticulospinal and raphespinal tracts (Huisman et al., 1981) and is involved in independent movements of individual upper limbs, especially their distal parts. The corticospinal pathway amplifies these various brainstem controls and, by means of its direct connections to motoneurons, provides the capacity to execute highly fractionated movements of the distal extremities (Kuypers, 1982).

Formulation of the Hypotheses

In Chapter 2, the methods used to acquire and analyze data will be discussed

in the context of their relevance to the experiments contained in this thesis.

In the chapters to follow, several hypotheses will arise out of a logical progression. Results from the first experiment will lead to a new hypothesis which will be tested and the results from that experiment will lead to the next hypothesis and so on. As such, all the experiments are related.

The first hypothesis was, "SBS activates alpha motoneurons differently than TCMS" with a sub-hypothesis being, "proximal limb muscles are recruited earlier and to a larger extent than intrinsic hand muscles", in accordance with activation of medial brainstem pathways that are involved in the activation of proximal limb muscles but not intrinsic hand muscles. An experiment was designed to examine the pattern of muscle activation after SBS in muscles known to receive strong excitation from the corticospinal pathway and muscles known to receive weak excitation. It was determined that muscles with weak excitation from the corticospinal pathway (ie. triceps) were recruited earlier and to a larger extent than muscles with strong excitation from the corticospinal pathway (ie. FDI) which is the opposite to what occurs after TCMS. It was concluded that SBS activated alpha motoneurons differently than TCMS by activating other descending pathways in addition to the corticospinal pathway. The conclusions were based on the premise that the muscle responses after

SBS were the result of activation of structures in the central nervous system and not stimulus current spread to peripheral nerve roots. The similarity between the pattern of muscle activation after SBS in humans and that after stimulation of non-corticospinal pathways in animals is discussed. The possibility that SBS directly activated cervical nerve roots to account for the results was not ruled out in this experiment.

To address this possibility, a second hypothesis was tested; "SBS does not activate muscles innervated below the level of the lesion in patients with complete cervical spinal cord injury". An experiment was designed where SBS was performed in three neurologically complete spinal cord injured patients with intact cervical nerve roots below the level of the lesion. No responses were recorded from muscles innervated below the level of the lesion in all patients despite normal peripheral nerve supply and deep tendon reflexes (DTRs) in those muscles. The SBS intensities used to determine the pattern of muscle activation in the first experiment were not sufficient to cause stimulus current spread to nerve roots. Accordingly, the order of muscle activation after SBS was due to activation of central motor pathways. SBS activated alpha motoneurons differently than TCMS. This may have been related, in part, to the different descending spinal cord volleys after SBS and TCMS.

This was investigated in the next two chapters where, for the first time, spinal cord evoked responses (SCEPs) and muscle responses were recorded after SBS and TCMS in awake normal subjects. The hypothesis was, "The SCEP after TCMS is different than that after SBS". To test this hypothesis, an experiment was designed to record SCEPs and muscle responses after SBS and TCMS in awake and anaesthetized human subjects. Recordings were obtained from neurologically intact subjects with dorsal column stimulators (DCS). SCEPs were recorded from the DCS. Multiple stimulus intensities were used. The SCEPs after TCMS and SBS had fast conduction velocities but the SCEP after SBS contained only one wave while that after TCMS had more waves and a longer duration.

TCMS was more effective than SBS in activating leg muscles at rest and leg muscle activation after TCMS was usually contingent on a SCEP that contained at least four waves. The second wave (I_1) contained in the SCEP after TCMS was usually recruited first but the first wave (D wave) could also be recruited first in combination with I_1. The amplitude of the later SCEP waves (I waves) after TCMS were more affected by anaesthetic agents than the D wave or the SCEP after SBS. It was concluded that the SCEP after SBS and TCMS were different. The waves after TCMS were similar to the D and I waves previously recorded from the spinal cord of anaesthetized monkeys after surface anodal

stimulation of the brain (Patton and Amassian, 1954).

It is argued that SBS was less discrete than TCMS and probably activated a wide variety of motor pathways at the skull base while TCMS with the stimulating coil positioned for maximum activation of the leg area probably activated the corticospinal pathway. The different pattern of muscle activation after TCMS was dependent on the area of cortical representation for a given muscle, the orientation and excitability of corticospinal neurons in that cortical area and the excitability of the spinal motoneurons while that after SBS was dependent on spinal mechanisms alone.

The role of cortical excitability versus the role of spinal motoneuron excitability in facilitation of muscle responses is a matter of debate (Day et al., 1987, Baker et al., 1995). Preactivation of a muscle or muscle group facilitates muscle responses following TCMS in awake subjects (Hess, 1986; Caramia et al., 1989; Pereon et al., 1995). The relationship between the SCEP and muscle responses after TCMS during rest and activation of a muscle has not previously been investigated. This lead to the hypothesis that, "Motor cortical excitability changes during facilitation of muscle responses". An experiment was designed where SCEPs and muscle responses were recorded after TCMS during muscle relaxation and then after voluntary activation of tibialis anterior (TA) at different

stimulus intensities. The SCEP rectified area was not significantly larger during voluntary activation of TA than at rest except at TCMS T. Voluntary activation of TA significantly increased the amplitude of all muscle responses compared to rest across all stimulus intensities.

Increased excitability of corticospinal neurons during voluntary activation of TA (indicated by increased SCEP rectified area) was observed at T but not at TCMS intensities above T. This suggested muscle facilitation could be partly related to increased excitability of corticospinal neurons as well as spinal motoneurons. New hypotheses related to the detection of increased corticospinal neuron excitability during voluntary muscle contraction at different TCMS intensities are discussed.

CHAPTER II

Methods

This chapter describes the main techniques used to acquire and analyze data. All experiments were approved by the Research Ethics Board at Sunnybrook Health Science Centre and all subjects gave their informed consent to participate in the experiments.

Percutaneous Electrical Stimulation At The Skull Base

The skull base was stimulated through two Grass EEG electrodes (1 cm diameter) fixed on either side of the scalp behind the mastoid process about five cm lateral to the inion (Fig. 1). This corresponded to position B described by Ugawa (Ugawa et al, 1991b). A head band was fashioned to hold the electrodes firmly in contact with the scalp and prevent electrode movement during stimulation. The skull base was stimulated using a cathode on the left and an anode on the right (Fig. 1). Capacitively coupled pulses (time constant 100 μs, 750 V maximum) were delivered from a Digitimer (Welwyn Garden City, Herts, UK) D180 stimulator at a rate of less than one every three seconds. The stimulating leads were kept away from the recording electrode leads and recording electrode headbox to prevent amplifier saturation due to stimulus artifact. Stimulus intensity was expressed as a percentage of the maximum output of the stimulator. The stimulator was externally triggered by a Cadwell Excel machine (Cadwell Laboratories Inc., Kennewick, WA). The capacitors in

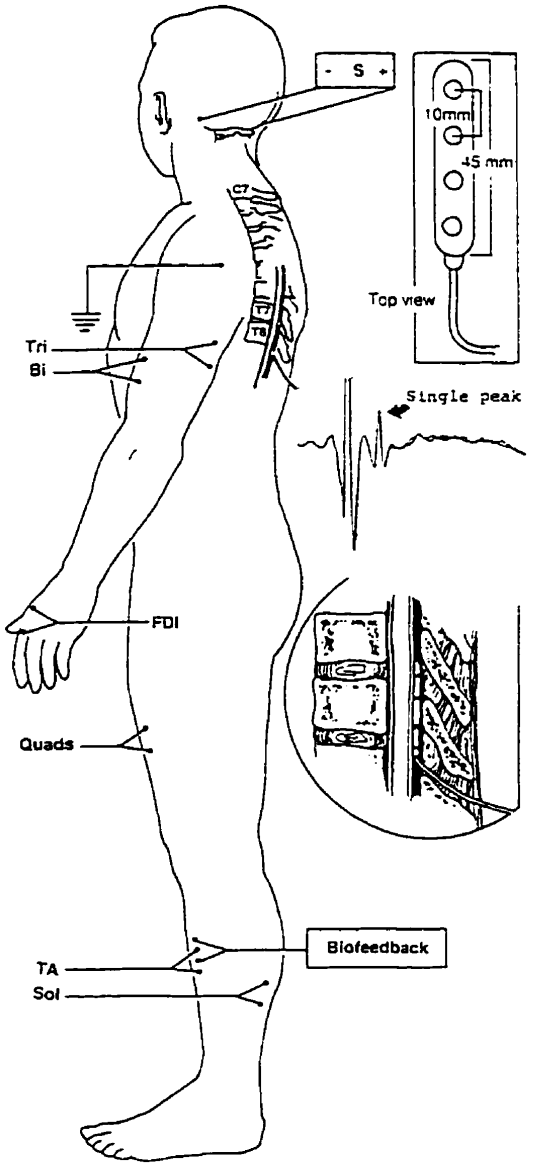


Figure 1. A schematic representation of the percutaneous electrical stimulation at the skull base technique. Stimulating electrodes (EEG surface electrodes, 1 cm diameter) were placed on either side of the scalp behind the mastoid at the level of the inion and connected to a Digitimer D180 stimulator (S). Muscle recordings were obtained from electrode pairs over the muscle belly of left triceps (Tri), biceps (Bi), first dorsal interosseous (FDI), quadriceps (Quads), tibialis anterior (TA) and soleus (Sol). Rectified EMG (biofeedback) was recorded from another pair of electrodes over the muscle belly of TA. Spinal cord recordings (middle insert on the right side of the figure) were obtained from a four-lead dorsal column stimulating (DCS) electrode (Medtronic Model 3586/3986) positioned in the posterior epidural space at the level of the body of T8 (top and bottom inserts on the right side of the figure). The most rostral DCS lead (tip of the electrode) was referenced to the lead 20 mm more caudal. In this subject, SBS produced a descending spinal cord evoked potential that contained a single peak (middle insert of the right side of the figure).

the stimulator were discharged 11.4 ms after the arrival of the external trigger pulse because the stimulator was triggered off the down going phase of the external trigger pulse as it returned to baseline. Occasionally, the recording instrument was externally triggered by the stimulator, and when this occurred there was no stimulus delay.

Transcranial Magnetic Stimulation

The brain was stimulated by a commercially available Novametrix (Novametrix Medical Systems Inc., USA) Magstim Model 200 (Fig. 2). Capacitors were rapidly discharged through a circular coil (internal diameter of coil was 5.4 cm, outer diameter was 11.6 cm consisting of 19 turns of copper wire) at a rate of less than one every three seconds. The stimulator and coil were positioned at the head of the bed away from the recording electrodes and amplifier headbox to reduce the recording of stimulus artifacts. The near-monophasic magnetic stimulator induced a current with a rapid rise to peak (100 μs) that decayed to zero in less than one ms. The magnetic field strength at the centre of the coil was approximately 1.5 Tesla. The largest induced current occurred 4.3 cm from the centre of the coil (middle of coil windings) in a plane parallel to the coil (Meyer et al., 1991).

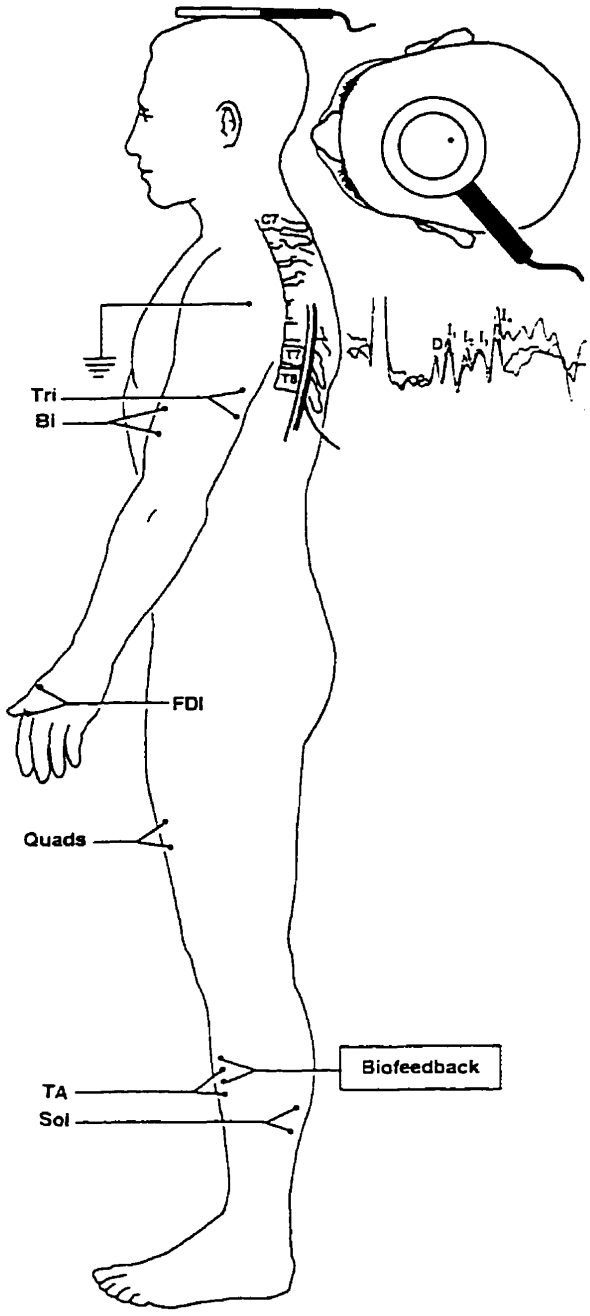


Figure 2. A schematic representation of the transcranial magnetic stimulation technique. The brain was stimulated by a Novametrix Magstim Model 200 with a standard circular coil (internal diameter of coil was 5.4 cm, outer diameter was 11.6 cm). Muscle recordings were obtained from electrode pairs over the muscle belly of left triceps (Tri), biceps (Bi), first dorsal interosseous (FDI), quadriceps (Quads), tibialis anterior (TA) and soleus (Sol). Rectified EMG (biofeedback) was recorded from another pair of electrodes over the muscle belly of TA. Spinal cord recordings were obtained from a four-lead dorsal column stimulating (DCS) electrode positioned in the posterior epidural space at the level of the body of T8. The most rostral DCS lead (tip of the electrode) was referenced to the lead 20 mm more caudal. In this subject, TCMS produced a descending spinal cord evoked potential that contained 5 peaks (D, I_1, I_2, I_3, I_4; bottom insert on the right side of the figure).

The position of the stimulating coil was measured from grid points that were marked on the scalp with a grease pencil on a line parallel to the nasion and vertex pre-auricular lines according to the 10 - 20 system (Jasper, 1958) such that the distance between points was 2 cm. Grid points were marked within a 4 cm radius of a point 4 cm anterior of Cz. When stimulating, the coil was laid flat and tangential to the skull surface with the current flowing in the coil in a clockwise direction (B side of the stimulator up). The centre of the coil was positioned over several scalp locations within the grid starting at the centre of the grid (4 cm anterior to Cz) which is, on average, the optimal position for activation of tibialis anterior (TA) (Ingram et al., 1988, Hess et al., 1991, Meyer et al., 1991). Resting motor threshold for TA for each subject was determined by increasing the stimulus intensity in three to five percent increments. The stimulus intensity was expressed as a percentage of the maximum output of the stimulator. The position that produced a TA response with minimum stimulus intensity was used in the experiment. The threshold for TA was the minimum stimulus intensity that produced at least three TA responses in six consecutive stimulations using a gain of 100μV per division (MacDonnell et al., 1991). The stimulator was externally triggered by a Cadwell Excel machine. The capacitors in the stimulator were discharged 9.73 ms after arrival of the trigger signal which was a function of the stimulator design.

Magnetic and Electrical Stimulation of Cervical Nerve Roots

For magnetic stimulation of cervical nerve roots, the standard circular coil was held tangential to the spine and centred approximately over the C4/C5 vertebrae. The largest induced current occurred 4.3 cm from the centre of the coil (Meyer et al., 1991). This position was appropriate for activation of C7, C8 and Th1 nerve roots near their exit from the spinal cord (Chokoverty et al., 1991, Maccabee et al., 1991) since these lower cervical nerve roots lie approximately 3 to 4 cm caudal to C5. The current in the coil flowed in a counter clockwise direction when viewed from behind the subject so the induced field flowed outwards along the left cervical nerve roots. Stimulus intensity was 100% of the maximum output of the stimulator.

Electrical stimulation of cervical nerve roots was performed using the D180 stimulator. A bipolar stimulating electrode (Model 922-6030-1, TECA Corp., Pleasantville, NY, USA) was placed over the C6 vertebrae in a rostro-caudal fashion (anode rostral) and stimulus intensity was increased until a maximal muscle response was obtained from triceps.

Muscle Recordings

Muscle responses were obtained from Grass EEG electrode pairs placed 3 cm apart over the muscle belly of biceps, triceps, first dorsal interosseous (FDI), quadriceps (Quad), TA and soleus (Sol) (Figs. 1 and 2). Recordings were limited to the muscles on the left side due to the number of available recording channels (eight). A ground plate electrode was placed on the shoulder. The impedance of the recording electrodes was kept below 3 Kohms. The recordings were amplified and displayed using either a Grass model 12 system and Tektronix dual beam storage oscilloscopes or a Cadwell Excel machine with a sampling rate was 48 kHz per channel. The sweep duration varied according to the study but usually ranged between 60 to 100 ms. The sweep time could be decreased to allow for accurate measurement of muscle response latencies. Usually muscle responses were stored on computer disc for later analysis but occasionally they were stored and analyzed on polaroid photographs obtained directly from the oscilloscope screen.

Stimuli were delivered to relaxed subjects lying supine on a bed. Subject relaxation was monitored by observing background EMG on the oscilloscope and by listening to it through an audio monitor connected to the amplifiers. Audio feedback from all channels was heard simultaneously. For low stimulus intensities, the amplifier gain was set at 100 μV/division to detect low amplitude responses. The recording bandpass was 30 - 5000 Hz. Amplifier gain was decreased to accommodate larger responses. Display scale was adjusted for

optimum presentation of waveforms.

Two compound muscle action potentials (CMAPs) from each muscle at each stimulus intensity were superimposed for waveform reproducibility. Onset latency and peak-to-peak amplitude were calculated from the average of the two CMAPs. The CMAP was expressed as a percentage of the maximum muscle response (M) obtained following supramaximal stimulation of its respective motor nerve. This was termed "relative amplitude" (% max M).

Electrical Stimulation Of Peripheral Nerves

Maximal muscle responses were obtained by strong electrical stimulation of peripheral nerves. The brachial plexus was stimulated at Erb's point for supramaximal biceps and triceps responses using a bipolar surface stimulating electrode (Model 922-6030-1, Teca Corp., Pleasantville, USA) connected to the constant current stimulator (Cadwell Laboratories Inc., Kennewick, WA). Similarly, the ulnar nerve was stimulated supramaximally at the wrist for FDI, the femoral nerve at the inguinal crease for quadriceps and the peroneal and posterior tibial nerves at the popliteal fossa for TA and Sol respectively. The cathode and anode were positioned along the long axis of the nerve with the cathode more distal.

F Responses

F responses were recorded from FDI and TA after supramaximal stimulation of the ulnar nerve at the wrist and the peroneal nerve at the popliteal fossa respectively. Ten F responses were obtained for each muscle and the F response with the shortest latency was used in the calculation of central conduction time.

Calculation Of Central Conduction Time After SBS

The latencies of the CMAPs for FDI and TA following SBS (T + 30% of the maximum output of the D180 stimulator), the latency of the M response and the shortest latency F wave (10 trials) for FDI and TA were used to calculate central conduction times as follows:

$$CCT^{(1)} = CMAP^{(2)} - \left[\left(\frac{F + M}{2}\right)^{(3)} + 1^{(4)}\right]$$

where $^{(1)}$ is conduction time from skull base to anterior horn, $^{(2)}$ is conduction time from skull base to target muscle, $^{(3)}$ is conduction time from anterior horn to target muscle and $^{(4)}$ is a 1 ms delay to account for the synaptic delay from upper motoneuron to lower motoneuron and the F response turn around time at the alpha motoneuron (Fig. 3) (Brouwer and Ashby, 1990; Rossini et al., 1994).

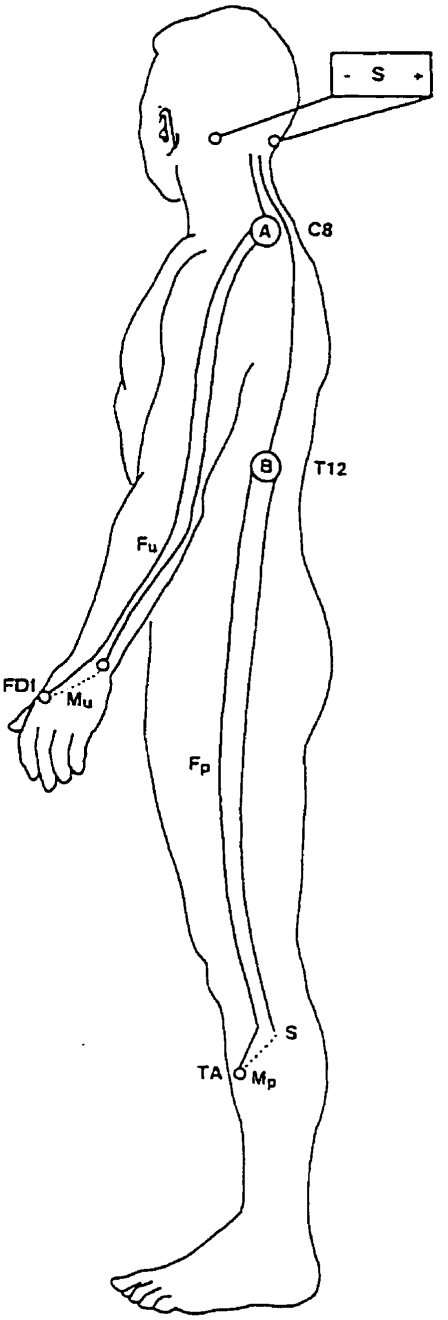


Figure 3: A schematic representation of the F response technique used for the calculation of central conduction time after percutaneous electrical stimulation at the skull base (SBS). The central conduction time is calculated by subtracting the peripheral conduction time to first dorsal interosseous (FDI) or tibialis anterior (TA), from the conduction time to those muscles after SBS (S). For example, the peripheral conduction time to TA is the F response latency to TA after supramaximal peroneal nerve stimulation at the popliteal fossa (F_p) plus the TA terminal latency (M_p) all divided by two, plus one millisecond to account for synaptic delay from the upper motoneuron to lower motoneuron, and the F response turn around time at the alpha motoneuron ("B" for TA, "A" for FDI). F_u is the F response latency to FDI after supramaximal ulnar nerve stimulation at the wrist. M_u is the FDI terminal latency.

The spinal cord conduction velocity in fastest conducting motor fibres was calculated by dividing spinal cord conduction time by the distance from the skull base to the C6 or L1 spinous process for each subject.

Electrical Stimulation Of Sternocleidomastoid

A bipolar surface stimulator (Teca, Pleasantville, USA) was positioned rostro-caudally over the belly of left sternomastoid (along the midline, 50% of the distance from its origin at the mastoid to its insertion at the xiphoid). Recordings were obtained from the muscles in the upper and lower extremities in the fashion described above.

Surgical Implantation Of The Dorsal Column Stimulating Electrode

Dorsal column stimulators were implanted for treatment of pain and not for the purpose of these experiments. Each patient was positioned prone then prepped and draped from the mid to lower thoracic spine. Local anaesthesia using 1% xylocaine without adrenalin was used to infuse the subcutaneous tissue and paravertebral muscles. Neuroleptic anaesthesia was also used. The paravertebral muscles were dissected from the spinous processes bilaterally through a midline incision. The inferior portion of the Th8 spinous process was removed and the ligamentum flavum was opened laterally between Th8 and Th9 to allow for insertion of the Medtronic dorsal column stimulator (Medtronic

Neurological, Model 3586 or 3986, Minneapolis, USA) cephalad in the epidural space at the level of the body of Th8 in all patients (Fig. 1). The Medtronic Model 3986 was a later version of the Model 3586 and had identical electrode specifications to the Model 3586. The DCS electrode contained four independent electrodes arranged in a silicone rubber strip and all four electrodes were in contact with the dura (Figs. 1 and 2). Electrode one of the DCS electrode array was most cephalad and electrode four was most caudad. The spinal cord was stimulated through the DCS electrode and the patient was questioned for sensations induced by stimulation. An attempt was made to place the electrode in the midline so that spinal cord stimulation induced paraesthesia from the lower back into the hips and lower extremities bilaterally. When the position of the electrode was satisfactory, the incision was closed in multiple layers. The electrode cable was tunnelled subcutaneously on the left side and passed through a small incision in the skin.

Spinal Cord Evoked Potential Recordings

The trial period for DCS was five to seven days during which time the cable from all four electrodes was externalized and connected to two bipolar mini phone jacks. Electrode one was connected to the tip of one phone jack and electrode three was connected to the other tip. The centre of electrodes one and three were separated by 2.0 cm on the spinal cord (Figs. 1 and 2). The diameter of electrode one and three was 4 mm and the surface area was 12 mm^2. For recording purposes, the two phone jack tips were connected to G1

(DCS electrode one) and G2 (DCS electrode three) of a differential amplifier (Cadwell Laboratories Inc., Kennewick, WA). In one subject, the SCEP was also recorded from DCS electrode one (G1) - skin surface at Th8 (G2) and DCS electrode three (G1) - skin surface at Th8 (G2). The surface electrode at Th8 was a Grass cup disc electrode (1 cm diameter) (Grass Instruments, Quincy, Massachusetts).

Intraoperative SCEP Recording

After the trial period, surgical internalization of the DCS apparatus was performed in the patients for whom DCS alleviated their pain. After induction of anaesthesia, inhalation agents (0.5% - 1.0% isoflurane, 55-66% N_2O, and O_2) were used to maintain a constant level of anaesthesia in the three subjects who participated in the intraoperative studies. Experiments were performed after the patients were on inhalation agents. For each patient, SCEP recordings were obtained from the same DCS electrode used in the awake experiments. Furthermore, for each patient, the recording variables and position of the stimulating coil or SBS electrodes were the same as those used in the awake experiment so the effects of anaesthesia on the SCEPs could be determined.

Biofeedback Techniques Used In the Facilitation Experiment

Voluntary activation of TA was maintained at 10% maximum voluntary

contraction as measured by an EMG biofeedback machine (Model 4081, Hyperion Inc., Miami, FL). The electrodes used for biofeedback were positioned 3 cm apart beside the TA recording electrodes already in position for recording muscle responses after TCMS or SBS (Figs. 1 and 2). The biofeedback machine provided auditory and visual feedback of rectified EMG to the subject. TCMS was delivered as soon as 10% maximum voluntary TA contraction was achieved.

Measurement of SCEP and Muscle Responses

The SCEP was the continuous average of three to five responses. A minimum of two averages were superimposed for waveform reproducibility. A grand average containing both SCEP averages (6 - 10 responses) was analyzed at each stimulus intensity. Each wave of the SCEP was measured for a) latency to the initial negative deflection, b) latency to negative peak, c) duration from the initial negative deflection of the first wave to the positive trough of the last wave, d) amplitude from onset to negative peak, e) amplitude from negative peak to next positive peak and f) SCEP rectified area (calculated by Digital Signal Processing software, Cadwell Laboratories Inc., Kennewick, WA) from the initial negative deflection of the first wave to the positive trough of the last wave. If the SCEP had more than one wave then the interwave latency was calculated between the wave onsets (initial negative deflection) and between the negative peaks of each wave.

For each muscle response, the onset latency and peak-to-peak amplitude were measured from the average of two responses. Typically, the muscle recordings were obtained at the beginning of each SCÉP average.

Statistical Analysis

The SCEP rectified area and muscle response amplitude obtained during rest were compared with those obtained during voluntary activation of TA at each stimulus intensity using a paired *t* test. The overall effect of voluntary activation of TA on SCEP area and the amplitude of muscle responses across all stimulus intensities was tested for significance by a repeated measures ANOVA. Where appropriate, the statistical procedures (*t* test, ANOVA) were repeated using the natural logarithm of SCEP area and muscle response amplitude. Post-hoc analyses of SCEPs and muscle responses were performed using a variety of statistical techniques suitable for the data acquired as described in each chapter.

CHAPTER III

Percutaneous Electrical Stimulation At The Skull Base In Normal Human Subjects

Abstract

Electrical stimulation over the skull base (SBS) can evoke muscle responses from the arms and legs. We investigated the pattern of muscle activation after SBS using a Digitimer D180 stimulator in 9 normal subjects. Electromyographic recordings were obtained from triceps, biceps, first dorsal interosseous (FDI), quadriceps, tibialis anterior and soleus at varying stimulus intensities. In all subjects, low SBS intensities recruited triceps (a muscle that receives weak corticospinal excitation) before FDI (a muscle that receives strong corticospinal excitation) which is opposite to the pattern of activation after transcranial magnetic stimulation (TCMS). Accordingly, SBS activated alpha motoneurons differently than TCMS.

High SBS intensities evoked responses from all muscles. The estimated percentage of the total alpha motoneuron pool being recruited for each muscle was higher for the upper limb than the lower limb at all stimulus intensities. Spinal cord conduction velocity was 75 m/s and 68 m/s in fastest conducting central motor pathways to upper and lower limb motoneurons, respectively.

Introduction

Muscle responses after transcranial electric stimulation (TCES) and transcranial magnetic stimulation (TCMS) are mediated primarily through the corticospinal tracts (Brouwer and Ashby, 1990; Boyd et al., 1986; Amassian et al., 1987) and probably cannot be used to directly assess the ventral funiculus. It is desirable to test anterior spinal cord pathways because they contain the vestibulospinal and reticulospinal pathways which play a role in posture and recovery of locomotion following spinal cord lesions (Yu and Eidelberg, 1981; Eidelberg et al., 1981, Vilensky et al., 1992).

Stimulation of motor pathways below the motor cortex has been performed in animals and to a limited extent in humans. Levy (Levy et al., 1986) directly stimulated the cerebellum (cerebellum - cerebellum or cerebellum - hard palate) in cats and recorded responses from spinal cord, peripheral nerve and muscle. Spinal cord lesioning studies revealed that the "cerebellar evoked potential (CEP)" recorded from the spinal cord was mediated by pathways in the dorsolateral and ventral cord and were separate from those pathways mediating the transcranial MEP. Pyramidal section did not change the CEP recorded from spinal cord or peripheral nerve. A similar CEP waveform could also be obtained following non-invasive stimulation over the skull base in cats (skull

base - hard palate) (Levy et al, 1986). From direct spinal cord recordings it was demonstrated that the CEP usually had a higher conduction velocity than the transcranial MEP. Levy concluded that the pathways activated by direct cerebellar stimulation may be the fast conducting vestibulospinal and reticulospinal pathways located in the ventral cord (Bantli et al, 1975; Bloedel and Bantli, 1978) or the rubrospinal pathway located in the dorsolateral cord in cats (Brodal, 1981).

Intraoperative CEP monitoring in humans was performed following direct cerebellar stimulation (cerebellum - hard palate) or indirect cerebellar stimulation (skull base - hard palate) (Levy et al, 1987). Recordings were obtained from spinal cord, peripheral nerve and muscle. The pathways being stimulated could not be accurately determined without lesion studies. Nevertheless, direct cerebellar stimulation resulted in nerve responses which were largest ipsilateral to side of stimulation. The CEPs, "sensitivity to injury was roughly similar to that of the MEP, but in some situations one changed more than the other", although it is unclear as to whether this comparison was based on spinal cord, peripheral nerve or muscle responses.

Hurlbert (Hurlbert et al., 1992) directly stimulated the cerebellum in rats (skull base - hard palate) and recorded the evoked responses from spinal cord and bilaterally from peripheral nerve and muscle regardless of the side of cerebellar

stimulation. The finding of bilateral responses from nerve and muscle is in conflict with Levy's finding of a primarily unilateral response from cat and human. This discrepancy can probably be accounted for by stimulus current spread throughout the brainstem and/or the entire cerebellum in Hurlbert's study due to the small size of the rat cerebellum. Threshold currents required to evoke thoracic cord, sciatic nerve and muscle responses in the rat were increasingly large so they concluded higher stimulus intensities activated progressively more remote structures. Spinal cord lesioning studies suggested that cord, nerve and muscle responses were probably mediated separately through reticulo/vestibulospinal, dorsal columns and cortico/rubrospinal pathways, respectively. It is interesting to note that the reticulo/vestibulospinal pathways had the lowest stimulus threshold for activation following direct cerebellar stimulation. Fehlings (Fehlings et al., 1991) concluded that the CEP in rat may have little to do with cerebellar activation and may simply reflect direct activation of brainstem nuclei such as the lateral vestibular nucleus.

Young (Young et al., 1980) directly stimulated the vestibular nerve and recorded the vestibular evoked potential from the spinal cord of cats. He recorded spinal cord and muscle responses and found that muscle responses were mediated by nearly every segment of the spinal cord from C2 to C8 and Th8 to Th12. Although no data are given regarding the pattern of muscle activation, he reports that, "primarily the trunk and proximal extensor limb

muscles", were activated.

Loud auditory clicks activated the saccule and generated neck muscle responses by way of vestibulospinal connections in human (Colebatch and Halmagyi, 1992). Single shock electric stimulation of Deiters' nucleus, excited limb extensor motoneurons and inhibited flexor motoneurons in cats (Maeda et al., 1975). Unfortunately, there are no reports of vestibulospinal evoked potentials from more distal muscles in humans that would be useful for intraoperative monitoring of ventral spinal cord function (Muto et al., 1995).

Percutaneous electrical stimulation at the skull base (SBS) is non-invasive and suitable for awake human subjects but the neural pathways activated by SBS in humans are not completely understood. Ugawa found that horizontally spaced stimulating electrodes placed at the skull base behind the mastoid at the level of the inion can activate descending motor pathways to the arm and leg muscles bilaterally (Ugawa et al., 1991b; Ugawa et al., 1992). Successful collision of a descending corticospinal pathway volley in the brain following transcranial electric stimulation over the motor cortex with an ascending volley in the brain following high intensity skull base stimulation provided evidence for corticospinal pathway stimulation following skull base stimulation. He estimated that SBS activated the corticospinal pathway near the cervico-medullary junction and this was confirmed in patients with neurological lesions (Ugawa et al.

1992). Neural pathway collision studies have shown that high intensity SBS activates at least the corticospinal tract near the pyramids of the medulla (Ugawa et al., 1991b). Their conclusions may have been biased toward the corticospinal pathway because they used the FDI response which receives strong projections from the corticospinal tract. The corticospinal tract preferentially excites small hand muscles (like FDI) but has little excitatory influence on biceps, triceps, or Sol motoneurons (Phillips and Porter, 1964; Brouwer and Ashby, 1990). Brouwer and Ashby (1990) showed that the pattern of muscle activation after TCMS reflects the relative strength of the corticospinal projections to spinal motoneurons. The pattern of muscle activation after SBS for muscles known to receive strong and weak projections from the corticospinal tract has not been previously determined in normal subjects.

TCMS activates the corticospinal pathway but SBS is less discrete and likely activates many ascending and descending spinal cord pathways in addition to the corticospinal tracts. For example, Ugawa and co-workers showed that SBS, timed to occur just before stimulation of the motor cortex, greatly diminished the FDI muscle response after TCMS. This suppression was absent or reduced in patients with dysfunction in the cerebellum or cerebellothalamocortical pathways. They concluded that SBS activated cerebellar structures that suppressed motor cortical excitability through a cerebellothalamocortical pathway (Ugawa et al., 1991a, 1994).

In summary, there are no non-invasive electrophysiological monitoring techniques that can evaluate long motor pathways other than the corticospinal tract in humans. In this chapter, SBS was performed in normal subjects to determine if the pattern of muscle activation in a wide range of muscles was different than that after TCMS.

Methods

Normative Study. Nine healthy volunteers (3 females, 6 males) aged 30 - 49 (mean = 34 years) participated in the study. The protocol was approved by the Research Ethics Board at Sunnybrook Health Science Centre and all subjects gave informed consent.

Stimulation and recording procedures were similar to those described by Ugawa (Ugawa et al. 1991b) and are described in detail in Chapter 2. The stimulus intensity was described as a percentage of the maximum output of the Digitimer D180 stimulator (750 V maximum) and the stimulus duration was 100 μs.

Muscle recordings were obtained from the surface of left triceps, biceps, FDI, Quads, TA and Sol in the fashion described in Chapter 2. Single stimuli were delivered at a rate not exceeding one every 3 seconds to relaxed subjects lying

supine on a bed. The stimulus intensity was gradually increased until a reproducible compound muscle action potential (CMAP) could be recorded from any of the muscles being studied. This stimulus intensity was termed "threshold" (T). The amplifier gain was set at 10×10^3 to detect low amplitude responses. Then the stimulus intensity was increased by 7.5% increments (7.5% maximum output of the stimulator) in 4 - 5 steps depending on the ability of the subject to tolerate the procedure. As the response got larger the amplifier gain for that muscle was decreased to accommodate the larger response.

Three of the nine subjects participated in the sternocleidomastoid (SCM) stimulation experiment. The muscle belly of SCM was stimulated as described in Chapter 2.

Results

The mean threshold for muscle activation was 24% of the maximum output of the stimulator (threshold range was 20-30%). All nine subjects were studied at each stimulus level up to T + 30% and eight of the nine subjects were studied up to T + 37.5% (one subject could not tolerate the T + 37.5%). Triceps was recruited first in all subjects and triceps and biceps were recruited at lower

stimulus intensities than FDI (Fig. 1). In general, muscles in the upper extremity were recruited at lower stimulus intensities than those in the lower extremity (Fig. 2). As the stimulus intensity increased from "threshold", the CMAP amplitudes from each muscle gradually increased. Biceps and triceps had a larger mean relative amplitude than FDI at all stimulus intensities. Overall, the mean relative amplitude was much greater for muscles in the upper extremity than in the lower extremity (Fig. 3).

SBS resulted in reproducible activation of all six muscles tested in seven of the eight subjects when stimulus intensities of up to T + 37.5% were used. A Quads and a FDI response was not obtained from one subject even at T + 37.5% stimulus intensity.

The mean onset latencies of the CMAPs for each muscle reflects the distance between stimulus and recording sites. Mean latencies to biceps, triceps, and FDI appeared to gradually decrease as higher stimulus intensities were used (Fig. 4). These muscles also had progressively larger relative amplitudes than the other muscles tested when higher stimulus intensities were used. When each muscle response was analyzed separately at each stimulus intensity for each subject, then sudden decreases in upper extremity muscle response latencies could be seen. An illustration of the finding is shown for triceps in figure 5. As SBS intensity increased from T + 22.5% to T + 30%, the amplitude

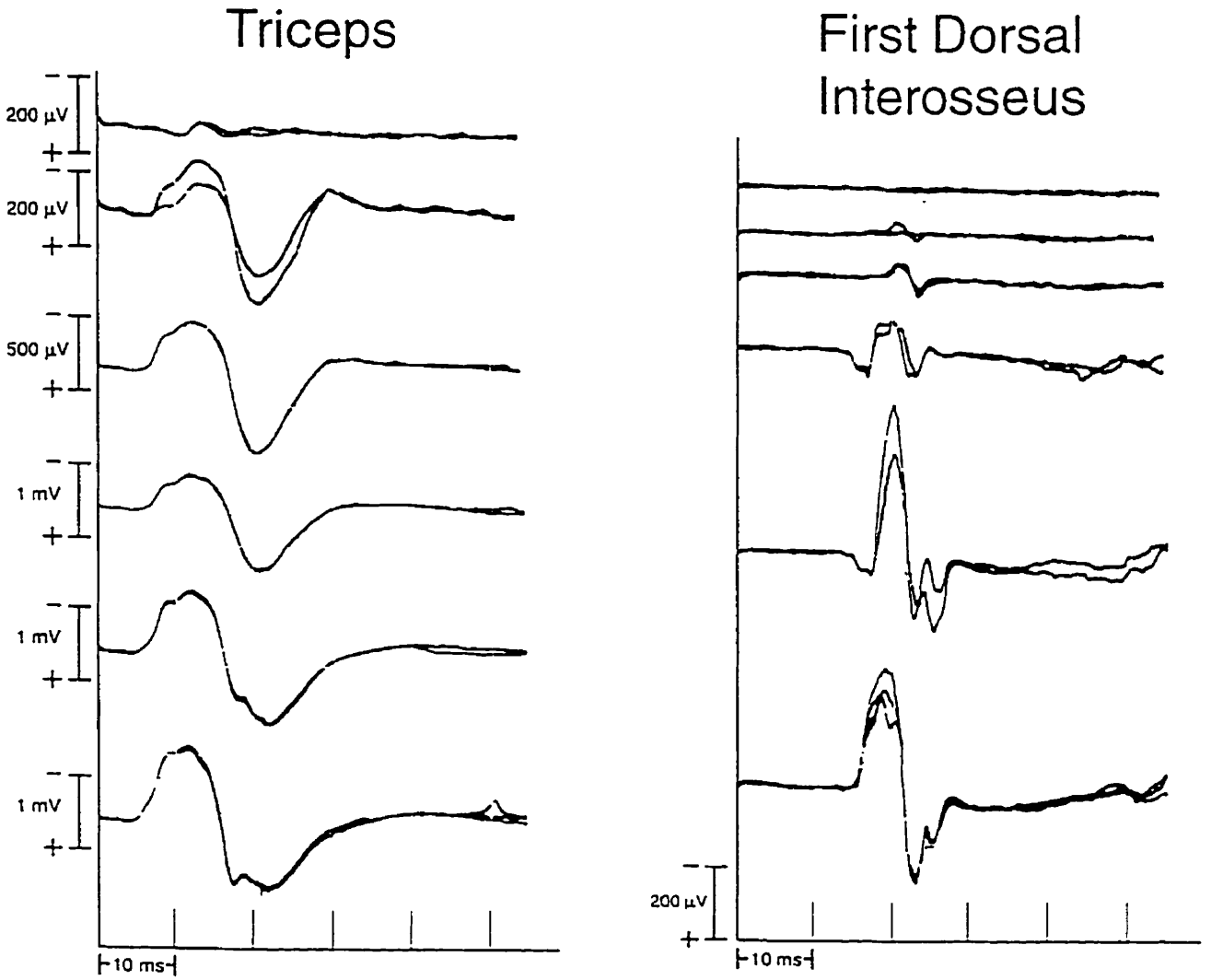
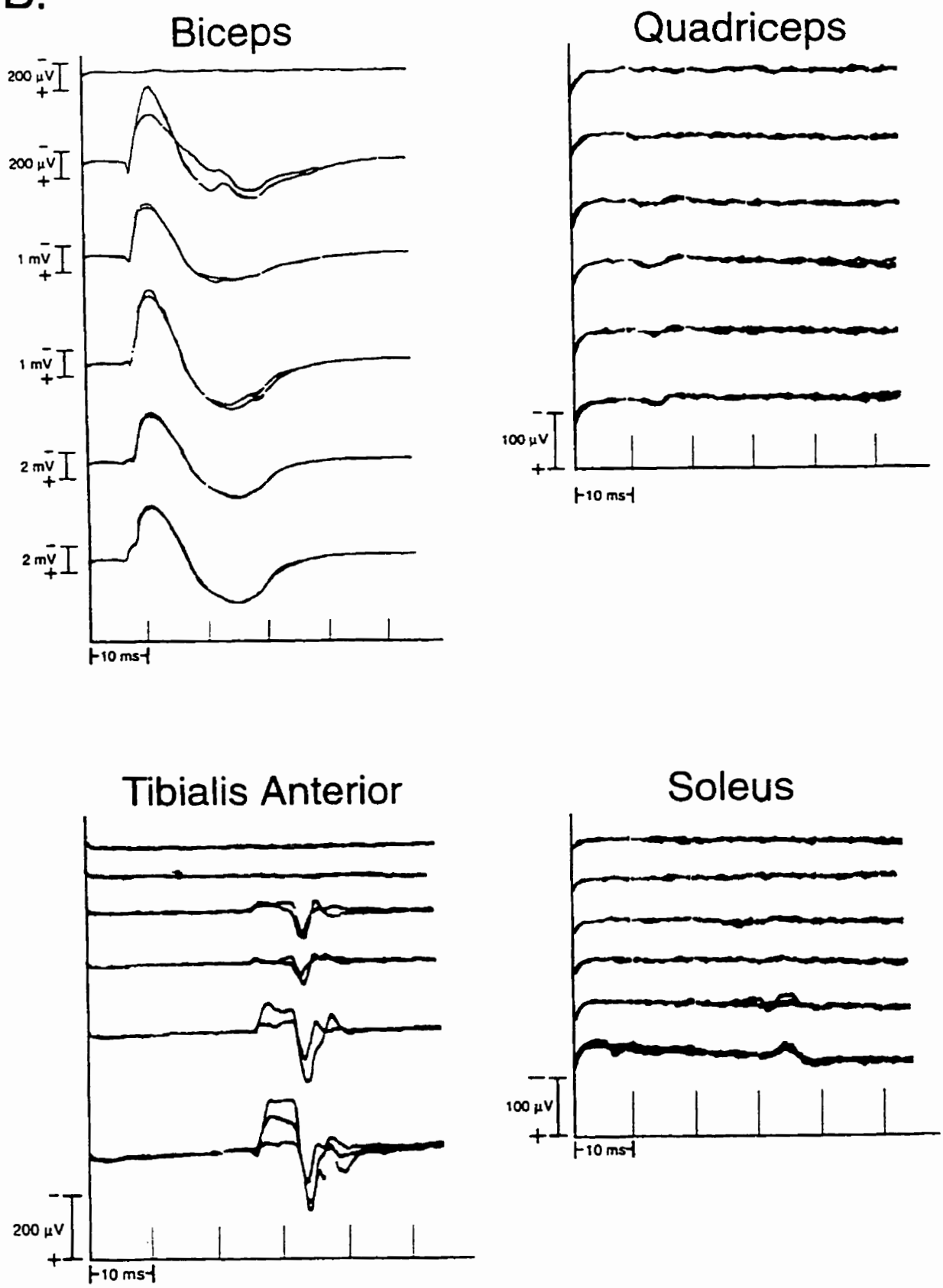


Figure 1: CMAPs recorded from **A.** triceps, first dorsal interosseous (FDI), **B.** biceps, quadriceps tibialis anterior and soleus in one subject following skull base stimulation at different stimulus intensities. The top trace of each graph was obtained at threshold (T) which was the lowest stimulus intensity that evoked a response from any of the muscles tested (triceps and biceps in this subject). The remaining five traces were obtained as stimulus intensity increased by 7.5% of the maximum output of stimulator (750V) in four steps to T + 37.5% (bottom trace of each graph). The stimulus was given at the beginning of the sweep. For each muscle response, two superimposed CMAP responses are shown. Triceps and biceps were recruited at lower stimulus intensities than FDI and had larger CMAP amplitudes than FDI at all stimulus intensities. Quadriceps and soleus had the smallest CMAP amplitudes.

B.


Biceps
200 µV
200 µV
1 mV
1 mV
2 mV
2 mV
10 ms
Quadriceps
100 µV
10 ms
Tibialis Anterior
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10 ms
Soleus
100 µV
10 ms

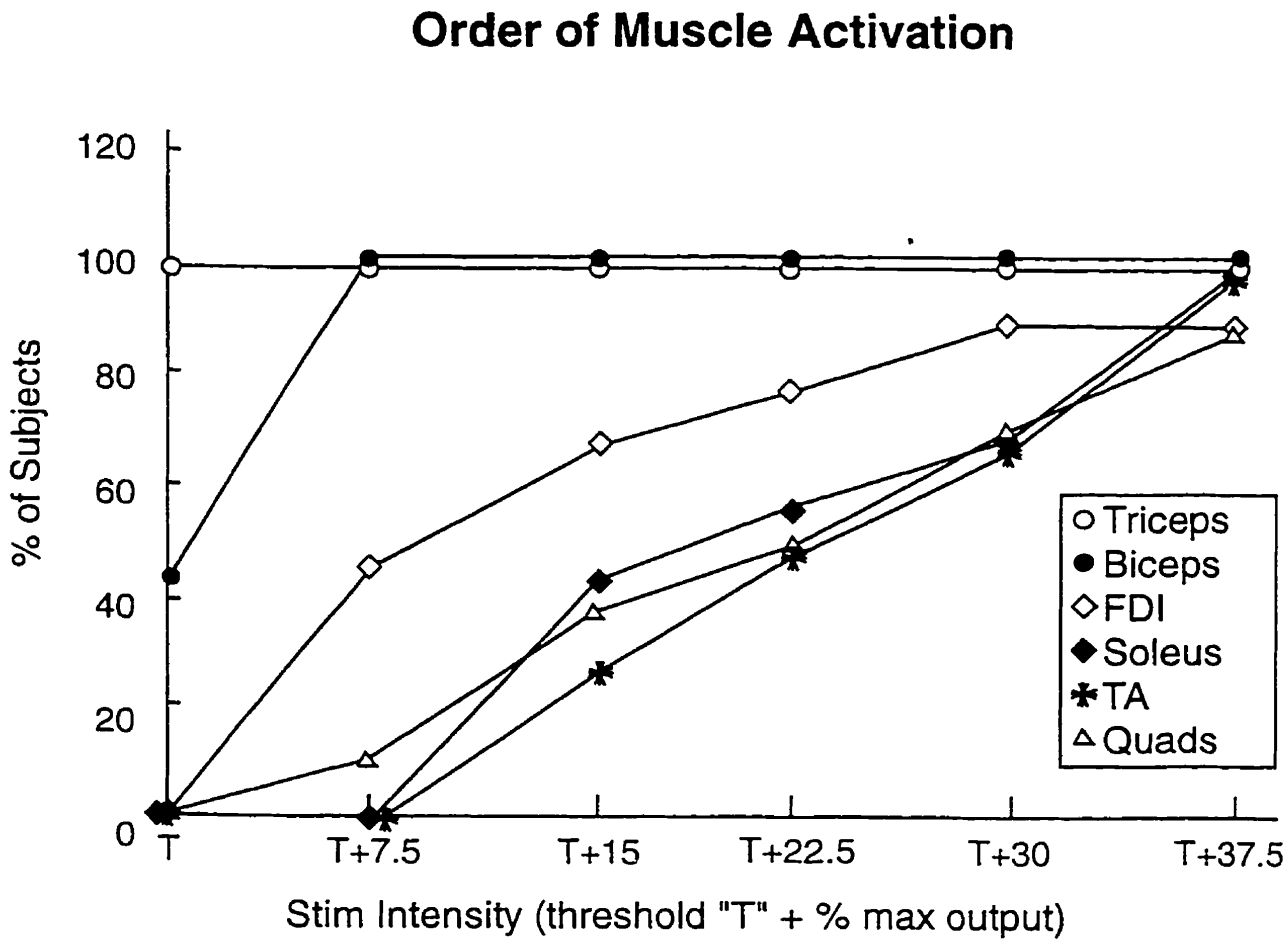


Figure 2: Order of muscle activation in 9 control subjects. Triceps was recruited first in all subjects. Muscle responses were obtained from a cohort of nine subjects at all stimulus intensities up to T + 30% and from eight of nine subjects at T + 37.5%. Overall, muscles in the upper extremity were recruited before those in the lower extremity.

A. **Mean Relative Amplitude of Muscle Response by Stimulus Intensity (Arms)**

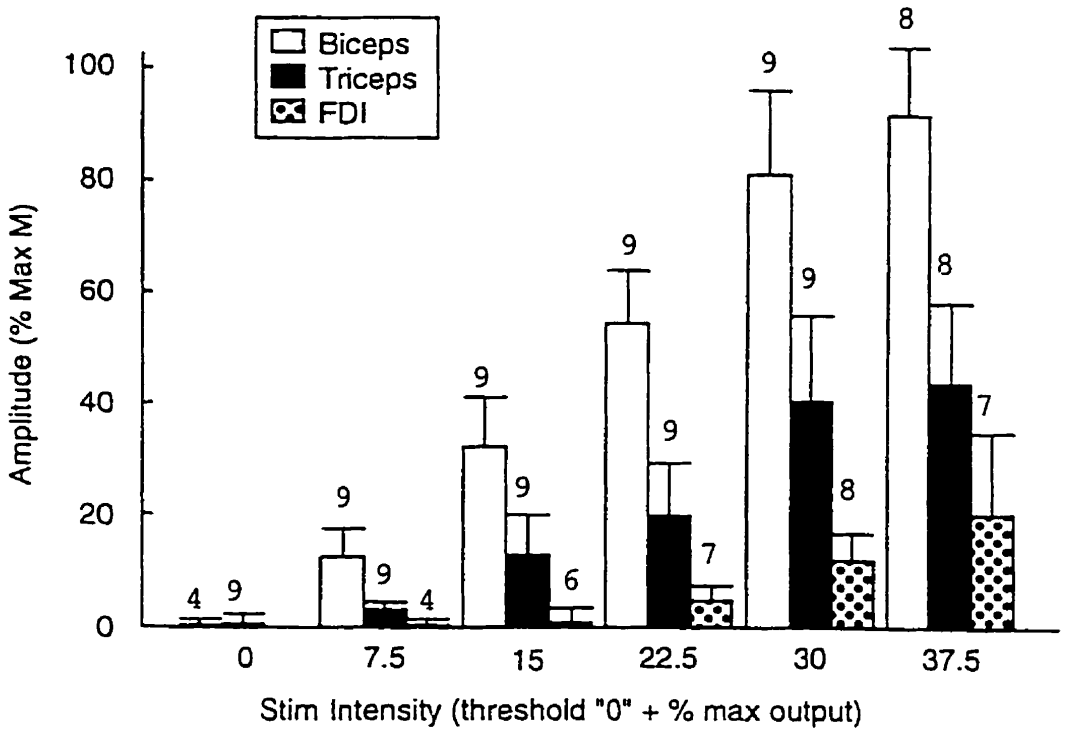
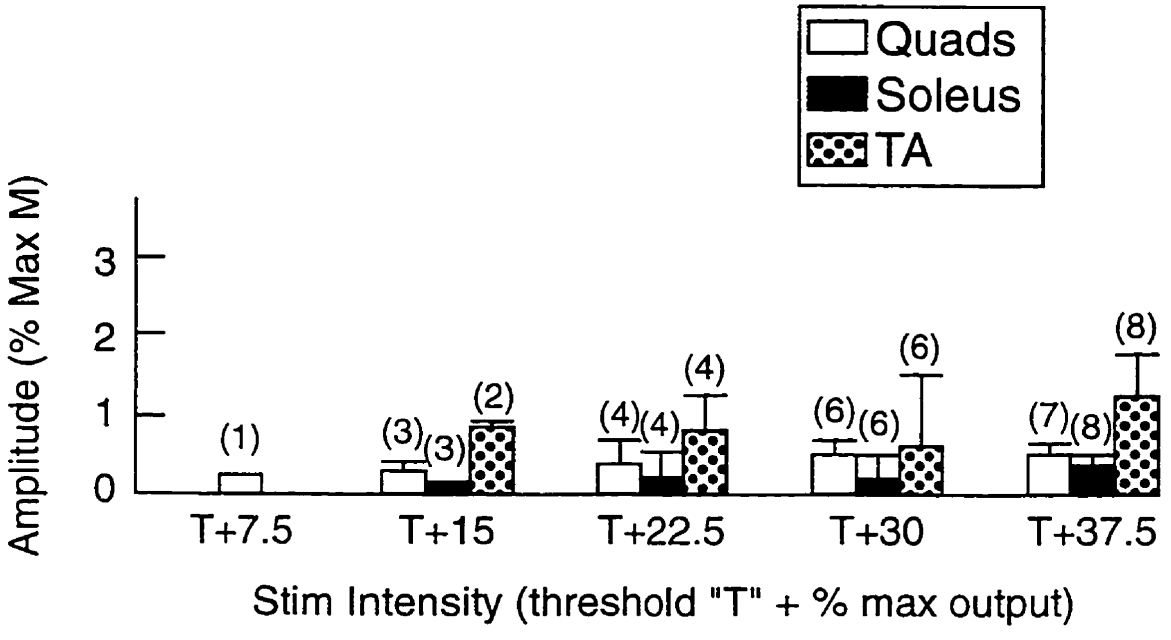


Figure 3: Mean relative amplitude (peak-to-peak voltage) of CMAP by stimulus intensity. Biceps and triceps had a larger mean relative amplitude than first dorsal interosseous (FDI) at all stimulus intensities. The mean relative amplitude (+ 1 S.E.) and the number of observations (above each bar) for **A.** left upper extremity muscles and **B.** left lower extremity muscles. Muscle responses were obtained from a cohort of nine subjects at all stimulus intensities up to T + 30% and from eight of nine subjects at T + 37.5%.

B.

Mean Amplitude of Muscle Response by Stimulus Intensity (Legs)



A.

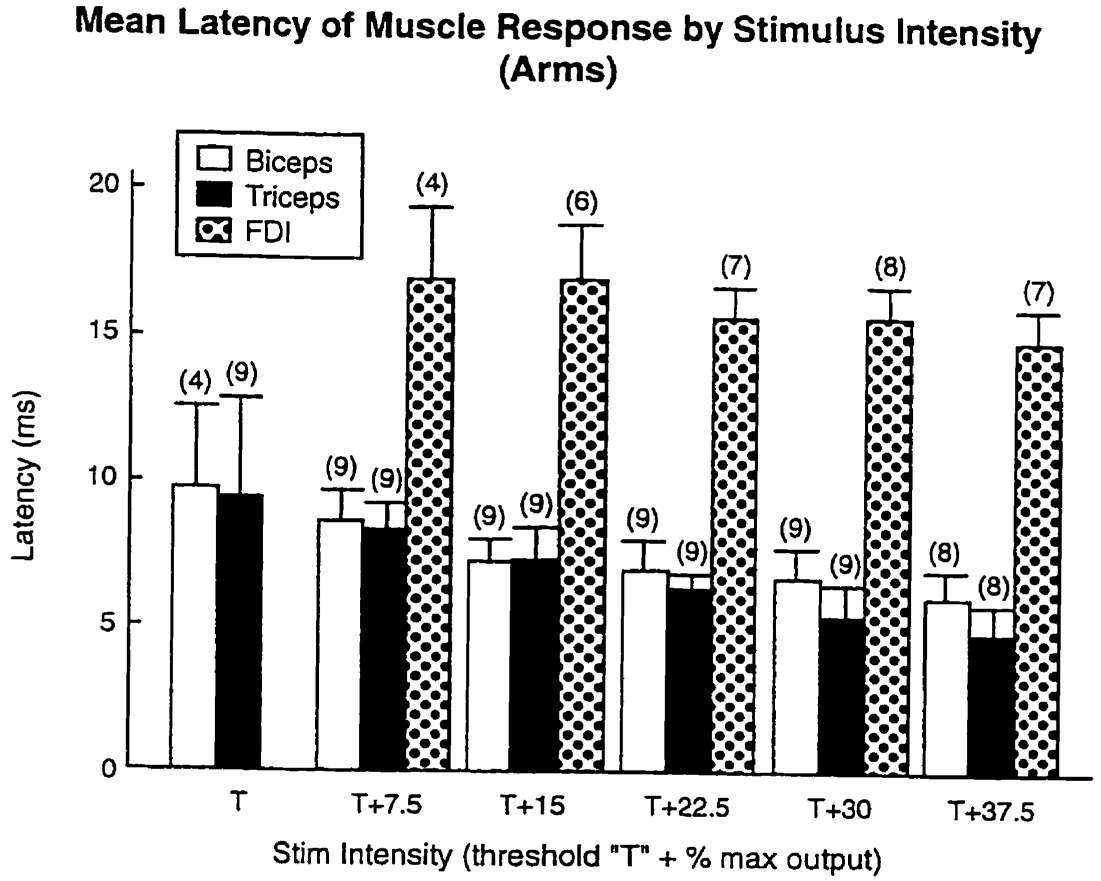
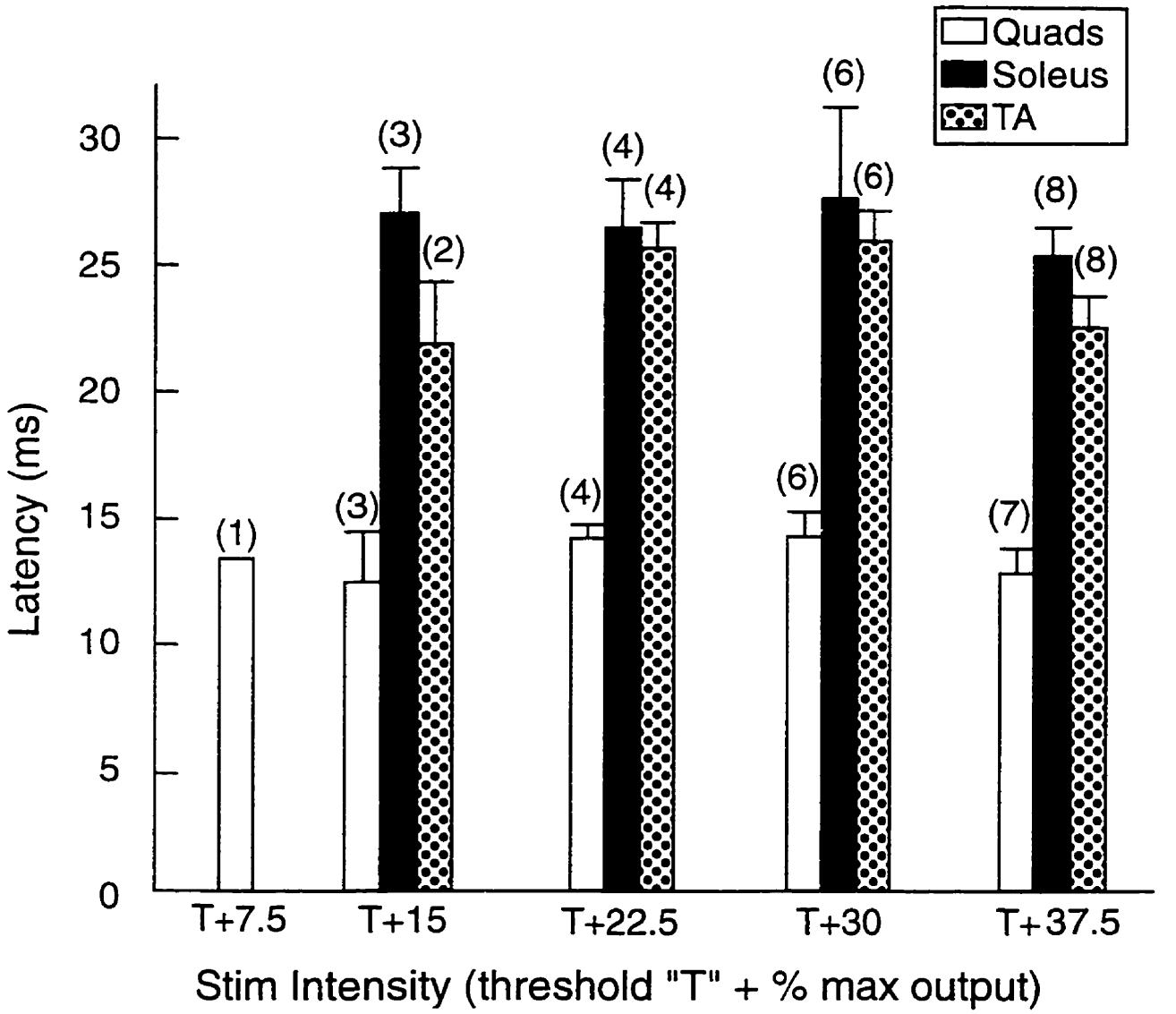


Figure 4: Mean latency (onset latency) of CMAP by stimulus intensity. Mean latencies (Arms) tended to become shorter as SBS intensity increased. The mean latency (+ 1 S.E.) and number of observations (in brackets) for **A.** left upper extremity muscles and **B.** left lower extremity muscles. Muscle responses were obtained from a cohort of nine subjects at all stimulus intensities up to T + 30% and from eight of nine subjects at T + 37.5%.

B.

Mean Latency of Muscle Response by Stimulus Intensity (Legs)



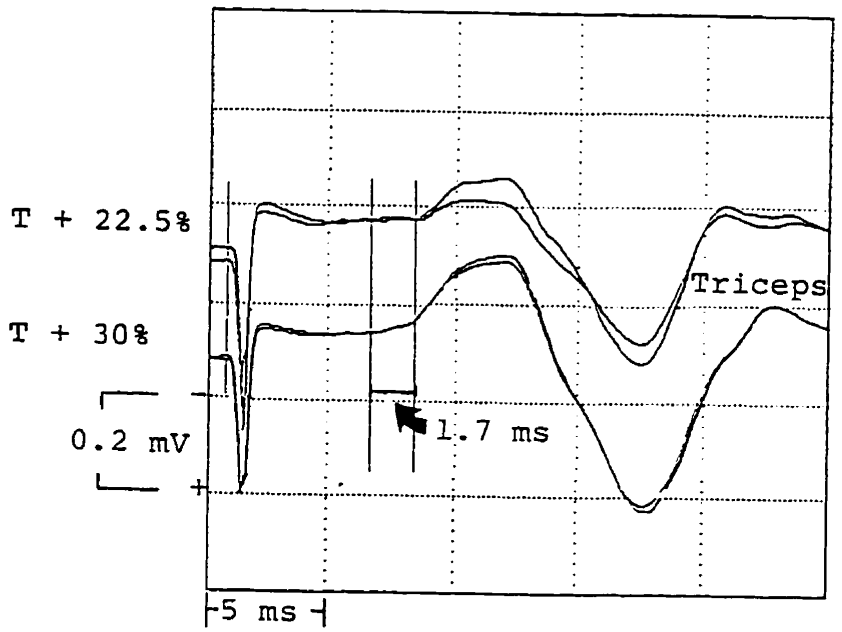


Figure 5: Changes in triceps CMAP amplitude and latency at increasing stimulus intensities in one subject. As stimulus intensity increased from T + 22.5% to T + 30% the amplitude of the triceps response got gradually larger and the latency decreased by 1.7 ms in a step-like fashion. At T + 30% the triceps latency after SBS was the same as that after lower cervical nerve root stimulation indicating stimulus current spread to C6/7 motor nerve roots.

of the triceps response got gradually larger and the latency decreased in a step-like fashion. Stimulation of the C6/7 motor nerve roots in this patient revealed that the triceps latency after SBS (T + 30%) was the same as that after motor nerve root stimulation. This indicated that stimulus current spread to C6/7 nerve roots occurred at T + 30% in this subject. Gradual decreases in triceps latency at stimulus intensities below T + 30% could occur without stimulus current spread to nerve roots (Fig. 1**A**, top two traces for Triceps).

In one subject, the FDI response latency after SBS at T + 50% was shorter than that after stimulation of lower cervical nerve roots indicating no SBS current spread to C8 and Th1 nerve roots even at high SBS intensities. In contrast, the triceps latency after SBS (T + 50%) and lower cervical nerve root stimulation was the same indicating stimulus current spread to motor C6/7 nerve roots supplying triceps in this patient (Fig. 6).

Direct stimulation of SCM muscle belly using a stimulus intensity that was three times SCM twitch threshold produced a local SCM contraction but did not activate any muscles in the upper and lower extremity in three of nine subjects who participated.

Spinal cord conduction velocity at T + 30% was estimated for FDI and TA in six of the nine subjects. The other three subjects did not have TA responses at T

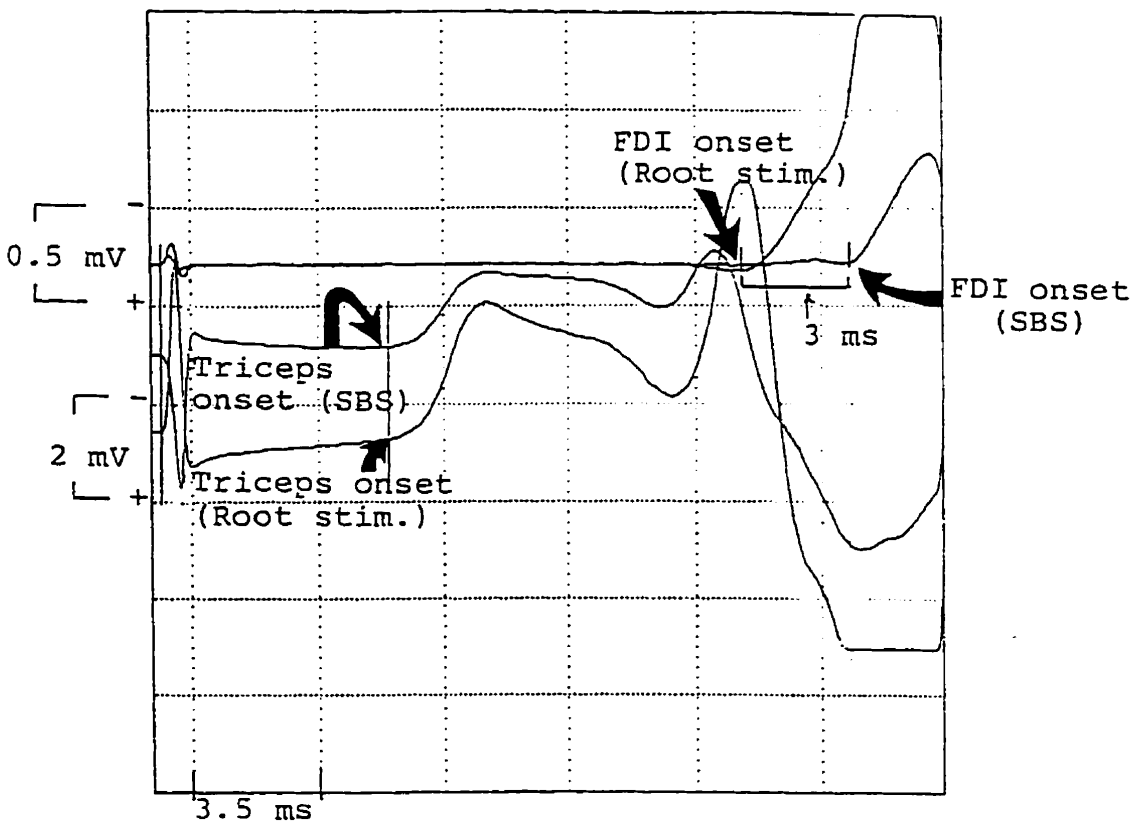


Figure 6: A comparison of the first dorsal interosseous (FDI) and triceps response latency after high intensity SBS (T + 50%) and electrical stimulation of lower cervical nerve roots in one subject. The triceps latency after SBS was the same as that after nerve root stimulation indicating stimulus current spread to C6/7 nerve roots. In contrast, the FDI response latency was 3 ms longer after SBS than after nerve root stimulation indicating no SBS current spread to C8 and Th1 nerve roots even at high SBS intensities. The 3 ms difference between SBS and nerve root stimulation is accounted for by a putative 1 ms synaptic delay from upper motoneuron to lower motoneuron and a 1 ms conduction time in proximal roots rostral to the site of electrical stimulation of nerve roots which leaves approximately 1 ms for central conduction time from skull base to anterior horn.

+ 30%. The mean distance from skull base to upper and lower alpha motoneuron pools was 114 mm and 465 mm respectively. The mean spinal cord conduction velocity was 75 m/sec to FDI (range 57 - 104 m/sec) and 68 m/sec to TA (range 59 - 73 m/sec). Estimates of mean peripheral and central conduction time without synaptic delay at the anterior horn cell are shown in Table 1.

Discussion:

We examined the order of activation of muscles known to receive strong excitation (FDI) or muscles known to receive weak excitation (triceps) from the corticospinal pathway (Phillips and Porter, 1964; Rothwell et al., 1987; Brouwer and Ashby, 1990) as stimulus intensity gradually increased. The CMAPs from triceps and biceps had lower thresholds for activation and greater relative amplitudes at all stimulus intensities than FDI. This is the opposite to what occurs after activation of corticospinal pathways following TCMS (Rothwell et al., 1987; Brouwer and Ashby, 1990) suggesting the relative strength of projections to spinal motoneurons (size of EPSPs) supplying triceps and biceps is greater after SBS than after TCMS. An explanation of this result may be that triceps and biceps were reflexively activated by stimulus current spread to neck muscle spindles. This was unlikely because direct stimulation of SCM failed to

TABLE 1. ESTIMATES OF MEAN PERIPHERAL AND CENTRAL CONDUCTION TIMES TO FIRST DORSAL INTEROSSEOUS (FDI) AND TIBIALIS ANTERIOR (TA) AFTER SBS IN 6 NORMAL SUBJECTS AT T+30%

	CMAP (ms)	PCT (ms)	CCT (ms)
FDI (mean±SD)	17.4 ± 1.3	14.9 ± 1.1	1.5 ± 0.5
TA (mean±SD)	25.3 ± 2.1	17.4 ± 1.4	7.0 ± 0.8

SD = Standard deviation

CMAP = Latency to muscle response after SBS

PCT = Peripheral conduction time

CCT = Central conduction time

activate biceps or triceps. Furthermore, spindle afferents entering the upper cervical spinal cord at one segmental level project mainly onto homonymous motoneurons of the same segment (Brink et al., 1988) Stimulation of cutaneous afferents and nerves supplying neck muscles mainly inhibit motoneurons of the dorsal neck muscles in cats (Anderson et al., 1977; Richmond and Loeb, 1992) and direct stimulation of nerves supplying neck muscles produced mainly inhibitory effects to those muscles. It is also possible that voluntary activation of triceps and biceps in anticipation of SBS may have facilitated these muscles but this was unlikely because background EMG was not detected on the oscilloscope or audio monitor during low intensity skull base stimulation when amplifier sensitivity was high (100 μV/division).

Ugawa used a collision experiment to show that SBS activated the corticospinal pathway at the base of the medulla (Ugawa et al., 1991b). Nevertheless, other pathways may have been activated after SBS because the success of a collision experiment is contingent on the activation of a single pathway at two different sites and does not preclude the activation of other pathways outside the one being tested in a collision experiment. SBS likely activated more pathways than TCMS so the difference in the pattern of muscle activation between SBS and TCMS may be related to the different net effect on the spinal motoneurons.

The corticospinal projections to the hand, wrist and finger extensors are stronger and more readily activated after TCMS and TCES than those to triceps and biceps in humans (Rothwell et al. 1987; Brouwer and Ashby, 1990) and subhuman primates (Phillips and Porter, 1964). One muscle group is activated before another because it has a larger number of cortical colonies projecting to its motoneuron pool (Landgren et al., 1962) and a higher density of cortical projections (Clough et al., 1968) so the poor activation of triceps and biceps after TCMS resulted from having fewer cortical colonies and a lower density of cortical projections than FDI. Phillips and Porter (1964) showed that cortical stimulation resulted in weak excitation of biceps and triceps motoneurons and inhibition of some triceps motoneurons. If the muscle responses after SBS resulted solely from activation of the corticospinal tract in the medulla then the FDI should have been more easily activated than triceps and biceps because it has a higher density of corticospinal fibres but this was not the case. The results from this chapter provide evidence that SBS activated spinal motoneurons differently than TCMS or TCES through fast conducting motor pathways. Activation of other motor pathways in addition to the corticospinal pathways may have accounted for these findings. The vestibulospinal, reticulospinal and rubrospinal pathways all have fast conduction velocities and may be readily activated by surface stimulation over the skull base in animals (Levy et al., 1986). It is also possible that antidromic activity in dorsal column fibres activated motoneurons through local reflex pathways in the cervical and

lumbar spinal segments but this contribution to muscle responses is likely to be small (Ugawa et al, 1995).

A progressively larger CMAP relative amplitude was associated with a progressively shorter CMAP latency to upper extremity muscles as stimulus intensity was increased. Ugawa (Ugawa et al., 1991b) showed that higher stimulus intensities could cause stimulus current spread to cervical roots. This was indicated by a distinct step decrease in CMAP latency. He recommended stimulating at the level of the inion (position B) to decrease current spread to motor nerve roots and increase CMAP amplitude. Accordingly, we stimulated at position B in all normal subjects. Nevertheless, the decrease in latency of triceps and biceps muscle responses at high SBS intensities was likely related to stimulus current spread directly to cervical nerve roots and the precise intensity at which this occurred was probably different for each subject. In contrast, the latency decreases observed when stimulus intensity increased at lower stimulus intensities can be explained by:

1. Stimulus current spread to activate the descending central motor pathways more caudally.
2. The recruitment of motoneurons that have axons with faster conduction velocities. This would be consistent with the size principle of motoneuron recruitment (Henneman et al., 1965).

3. Recruitment of other motor pathways with faster conduction velocities at higher stimulus intensities.
4. Decreased rise time of EPSPs due to increased magnitude of excitatory input to alpha motoneurons.
5. Undetected background muscle activity. Voluntary activation of muscles during SBS may have shortened the latency and increased the amplitude of evoked muscle responses by recruiting more spinal motoneurons with faster conducting inputs. Motoneurons receive multiple excitatory inputs which can be temporally dispersed so voluntary activation may have brought the motoneuron closer to threshold making it more likely to fire (Day et al., 1987; Rothwell et al., 1987). Undetected voluntary activation of target muscles at lower SBS intensities was unlikely in this experiment because background EMG was not detected on the oscilloscope or audio monitor at a time when amplifier sensitivity was high. In contrast, activation of muscles at higher stimulus intensities may have gone undetected because the amplifier sensitivity necessary to detect background EMG was decreased to accommodate the larger muscle responses.

In this chapter it was demonstrated that SBS activated triceps and biceps at lower stimulus intensities and to a greater extent than FDI which is the opposite to what happens after TCMS. Accordingly, the relative strength of projections

to spinal motoneurons supplying triceps and biceps was greater after SBS than after TCMS. SBS may have activated other motor pathways in addition to the corticospinal pathway to account for these findings but the evidence is necessarily indirect as it is impossible to perform lesioning studies or stimulate and record from specific spinal tracts in normal human subjects.

Stimulus current spread to cervical nerve roots, as a contaminating factor in the interpretation of our results, was not totally ruled out although it was unlikely to have occurred at the low SBS intensities we used to determine the order of muscle activation. The next chapter will demonstrate that the muscle responses after low intensity SBS are the result of CNS activation and not stimulus current spread to cervical nerve roots.

CHAPTER IV

Percutaneous Electrical Stimulation At The Skull Base In Neurologically Complete Spinal Cord Injured Patients With Intact Peripheral Nerves

Abstract

Electrical stimulation over the skull base (SBS), using a Digitimer D180 stimulator, recruits triceps (a muscle that receives weak corticospinal excitation) before FDI (a muscle that receives strong corticospinal excitation). The possibility that this order of recruitment is caused by stimulus current spread to cervical nerve roots has not been ruled out. To address this possibility, SBS was performed in three neurologically complete spinal cord injured patients with intact C7, C8 and Th1 nerve roots below the level of the lesion.

Muscle recordings were obtained from left deltoid, biceps, triceps, FDI, TA and Sol. SBS threshold (T) was the stimulus intensity that recruited the first muscle response above the level of the lesion. The SBS intensity was increased by 7.5% increments up to T + 22.5%. No responses were recorded from muscles innervated below the level of the lesion in all patients and at all SBS intensities despite normal peripheral nerve supply in those muscles (verified by magnetic stimulation of nerve roots). Accordingly, SBS (up to T + 22.5%) did not cause stimulus current spread to C7, C8 and Th1 nerve roots that was sufficient to excite motor axons in these patients. This verifies that the pattern of muscle activation after SBS is due to activation of central motor pathways that excite alpha motoneurons differently than TCMS.

Introduction

The previous chapter described the pattern of muscle activation after SBS. Triceps was activated at lower stimulus intensities before FDI in all subjects which is the opposite to what happens after TCMS. Furthermore, triceps % max amplitude was higher than the FDI % max amplitude at all SBS intensities which is the opposite to what happens after TCMS. The difference in muscle recruitment pattern and amount of muscle activation between SBS and TCMS suggests SBS activated alpha motoneurons differently than TCMS but it is also possible that stimulus current spread to high cervical nerve roots after SBS accounted for the early and large recruitment of triceps. Ugawa (Ugawa et al., 1991) demonstrated that when SBS intensity increased from 50% to 60% of the maximum output of the Digitimer D180 stimulator then the latency of the biceps CMAP shortened in a step-like fashion indicating activation of cervical nerve roots at 60%. 60% of the maximum output of the stimulator is equivalent to T + 37% described in the previous chapter (mean T was 24% in Chapter 3). Nevertheless, it is still possible that the early and large recruitment of triceps after low intensity SBS in our study may have resulted from stimulus current spread to the C6 and C7 nerve roots. The C8 and Th1 nerve roots supplying FDI would be less likely to be activated by stimulus current spread at low SBS intensities because they are farther away from the SBS. Stimulus current spread to nerve roots was possible in our study because of the high voltages

required to evoke muscle responses and the proximity of the SBS electrodes to the cervical nerve roots. In order to assess the role of stimulus current spread to cervical nerve roots after SBS we studied neurologically complete high cervical spinal cord injured patients with intact C7 nerve roots.

Methods

Patient Population: Three patients with complete cervical spinal cord injury participated in the study. The neurological level of their injuries was C5, C6 and C2 respectively. All patients had no sensation below the level of the lesion. All patients had Medical Research Council (MRC) grade 0/5 power in hand intrinsics, grip and elbow extension bilaterally. The C6 spinal cord injured patient had grade 3 elbow flexion and grade 5 arm abduction bilaterally. The C5 spinal cord injured patient had grade 1 elbow flexion and grade 1 arm abduction bilaterally. The C2 spinal cord injured patient had 0/5 power in arm abduction, elbow flexion, and elbow extension bilaterally. None of the patients had voluntary left triceps function but all had intact left triceps deep tendon jerks. All gave informed consent and all were tested more than 4 weeks after spinal cord injury (mean = 9.8 weeks).

SBS studies: Muscle recordings were obtained from surface electrodes placed

3 cm apart over the muscle belly of left deltoid, biceps, triceps, FDI, TA and Sol in all subjects. SBS stimulating and recording parameters were the same as those described in Chapter 2. Threshold (T) was the stimulus intensity that recruited the first muscle response above the level of the lesion. The patient with the C2 spinal cord injury had T arbitrarily determined as the mean T previously derived from normal subjects (23% of maximal output of the stimulator) because there were no arm muscles to be activated above the level of the lesion in this patient. The stimulus intensity was increased by 7.5% increments up to T + 22.5% in all subjects. SBS intensities higher than T + 22.5% were not used because they produce head movements that are contraindicated in patients who are recovering from unstable neck fractures. The subjects were supine during testing.

Motor Nerve Conduction Studies: The cervical nerve roots were magnetically stimulated to verify that the left C7 nerve root was intact. The coil position was optimal for lower cervical root stimulation on the left side as described in Chapter 2.

Results

All 3 cervical spinal cord injured patients had intact C7 nerve roots as verified

by intact deep tendon jerks from triceps and present triceps CMAPs after magnetic stimulation of cervical nerve roots. Nevertheless, SBS failed to activate triceps and FDI in all patients even at T + 22.5% (mean T was 31% of the maximum output of the stimulator). For example, the patient with C2 spinal cord injury had no muscle responses after SBS despite present triceps, biceps and FDI responses after magnetic stimulation of cervical nerve roots (Fig. 1). In the C6 spinal cord injured patient, deltoid and biceps were activated after SBS (T for biceps was 40% of the maximum output of the stimulator) but SBS intensities up to T + 22.5% failed to activate triceps and FDI. In the C5 spinal cord injured patient, only deltoid was activated after SBS (T for deltoid was 30% of the maximum output of the stimulator). At SBS intensity T + 22.5% stimulus current spread to the C5 motor nerve root was likely because the latency of the deltoid response was similar to that after cervical nerve root stimulation (Fig. 2). Nevertheless, SBS at T + 22.5% failed to activate biceps, triceps and FDI in accordance with the patients inability to voluntarily activate those muscles.

Discussion

The SBS intensities used in the previous chapter to determine the pattern of muscle activation were appropriate for activating central motor pathways. This was verified when SBS (up to T + 22.5%) failed to activate triceps in 3 patients

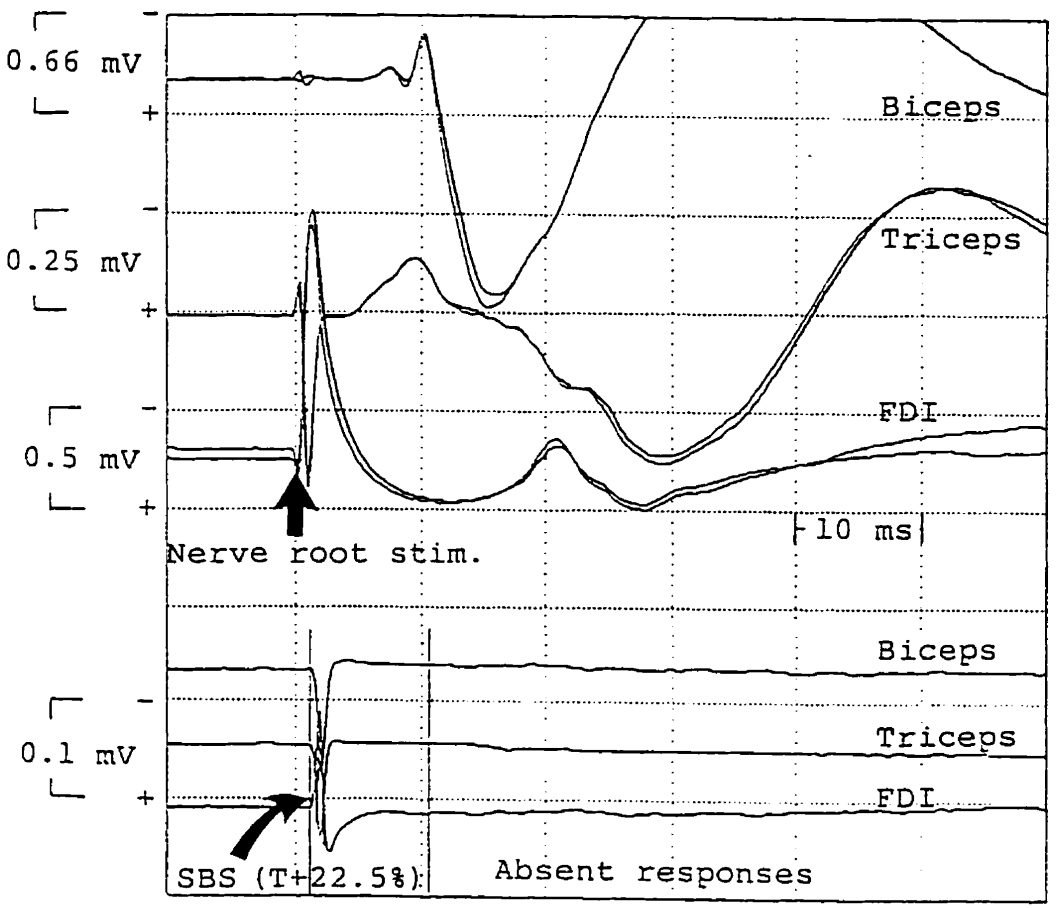


Figure 1: Magnetic stimulation of cervical nerve roots (top three traces) and percutaneous electrical stimulation at the skull base (SBS) in a patient with a neurologically complete C2 spinal cord injury and intact deep tendon reflexes from left biceps and triceps. Stimulation of cervical nerve roots activated left biceps, triceps and first dorsal interosseous (FDI) muscles. In contrast, SBS (T + 22.5%) failed to activate those muscles indicating no SBS current spread to nerve roots.

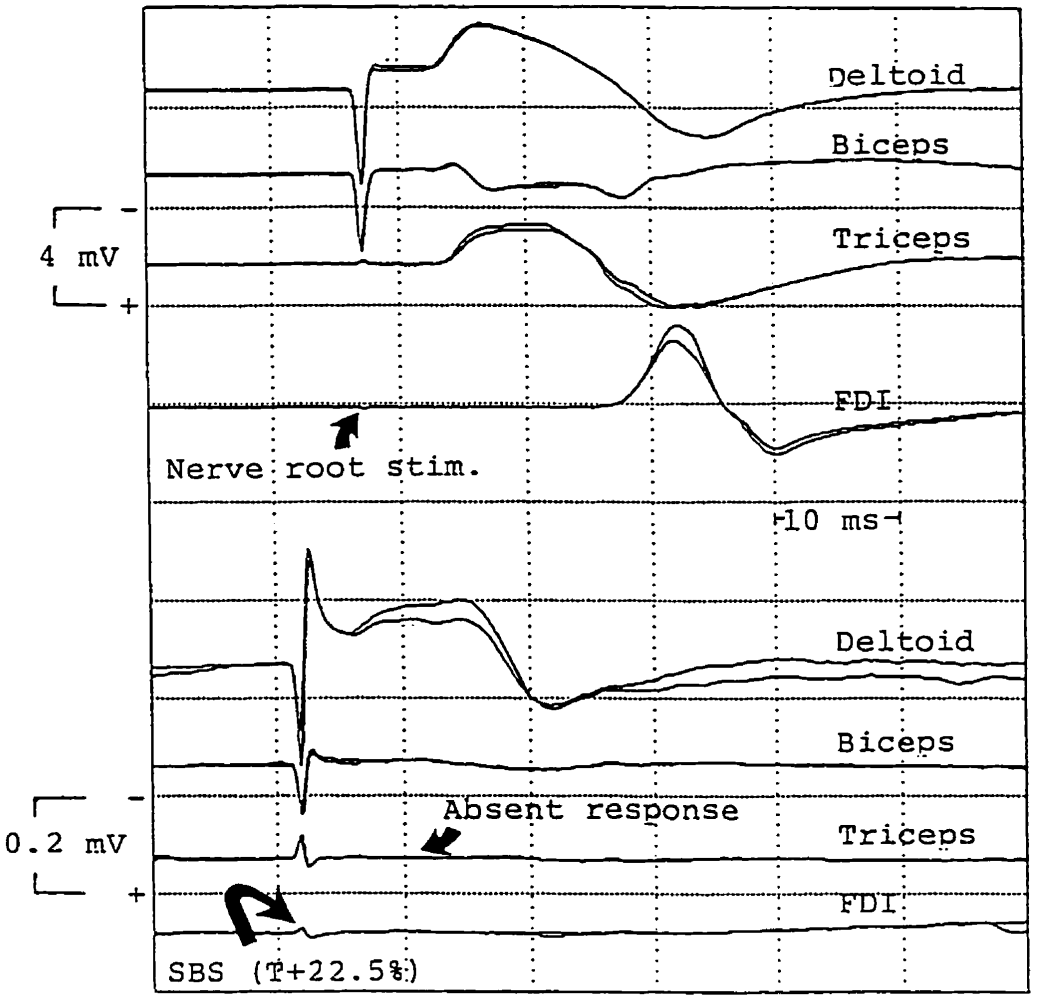


Figure 2: Magnetic stimulation of cervical nerve roots (top four traces) and percutaneous electrical stimulation at the skull base (SBS) in a patient with a neurologically complete C5 spinal cord injury and intact deep tendon reflexes from left triceps. Stimulation of cervical nerve roots activated left deltoid, biceps, triceps and first dorsal interosseous (FDI) muscles. The deltoid response after SBS (T + 22.5%) was likely caused by stimulus current spread to the C5 nerve root because it had a similar latency to that after cervical nerve root stimulation. In contrast, biceps, triceps and FDI were not activated after SBS indicating no SBS current spread to C7, C8 and T1 nerve roots.

with complete cervical spinal cord injuries whose injury level was above an intact C7 nerve root. In contrast, our previous study demonstrated that 100% of normal subjects had a triceps response at T + 22.5%, and the triceps responses had a large mean relative amplitude (see Chapter 3).

Biceps and deltoid were used to determine T in 2 patients but the third patient (C2 spinal cord injury) had T arbitrarily determined at 24% of the maximum output of the stimulator because no limb muscles could be evoked after SBS. In normal subjects, triceps was always used in the determination of T because it had the lowest threshold for activation, but triceps was not activated in these patients with high cervical spinal cord injury. Accordingly, T was determined from other muscles (biceps, deltoid) that were activated after SBS in the patients with spinal cord injury. The mean T SBS intensity was higher in the patients with spinal cord injury than normal subjects (33% versus 24% respectively) so the absent triceps responses after SBS at T + 22.5% in the patients with spinal cord injury was not likely due to inadequate SBS intensity. Instead, it was absent because the descending spinal cord volley after SBS was blocked by the spinal cord injury before it could reach the alpha motoneuron pool supplying triceps.

Having ruled out the role of stimulus current spread as a confounding factor in the interpretation of our results from Chapter 3, it can be said that, in normal

subjects, SBS activated alpha motoneurons differently than TCMS because triceps was recruited earlier than FDI after SBS in all nine subjects which is opposite to what happens after TCMS or TCES (Rothwell et al., 1987; Brouwer and Ashby, 1990). Activation of other motor pathways in addition to the corticospinal pathway after SBS may explain the results.

Differences in the descending volleys after SBS and TCMS, regardless of the pathway(s) through which they are mediated, may also explain why SBS and TCMS activate alpha motoneurons differently. The SCEPs after SBS and TCMS have not been recorded in awake humans but, in anaesthetized humans it has been demonstrated that SBS activates long tracts in the medulla and/or high spinal cord resulting in a descending volley containing a single wave of depolarization (Rothwell et al., 1994). Rothwell et al. (1994) demonstrated that the SCEP after SBS had a stable duration as SBS intensity increased so increases in spinal motoneuron depolarization with increasing SBS intensity are likely to be more reliant on increases in SCEP amplitude than on an increase in the number of waves contained in the SCEP. In contrast, the SCEP after TCMS in anaesthetized humans contains multiple waves (Thompson et al., 1991) that may depolarize alpha motoneurons by way of temporal summation (Day et al., 1987) since neuronal depolarization is dependent on both the amplitude and duration of the volley that arrives at the cell membrane.

The following chapter will characterize the SCEP after SBS. The chapter after that will characterize the SCEP after TCMS and compare it to that after SBS.

CHAPTER V

Spinal Cord Evoked Potentials And Muscle Responses After SBS In Awake Human Subjects

Abstract

Spinal cord evoked potentials (SCEPs) were recorded from epidural dorsal column stimulators at Th8 after percutaneous electrical stimulation at the skull base in six awake, neurologically intact human subjects. Muscle recordings were concomitantly recorded from the left biceps, triceps, first dorsal interosseous, tibialis anterior (TA) and soleus while the subjects were at rest. Threshold (T) for activation of the SCEP varied between 20 and 35% of the maximum output of the Digitimer D180 stimulator (750V). The stimulus intensity was increased by 7.5% increments (7.5% of the maximum output of the stimulator) to T + 22.5% in 3 steps. The SCEP had one negative peak at all stimulus intensities and evoked muscle responses from the upper extremity in all subjects and from the lower extremity in three of the six subjects. The SCEP amplitude and rectified area greatly increased with increasing stimulus intensity but the SCEP latency did not greatly change. The mean SCEP conduction velocity after SBS was 94 m/sec (range 80 - 103 m/sec).

Three subjects performed ankle dorsiflexion (10% maximum voluntary activation of TA) during SBS (T + 22.5%), which resulted in facilitation (increased amplitude and decreased latency) of all muscle responses (legs more than arms) without changing the SCEP amplitude or rectified area.

Introduction

High intensity percutaneous electrical stimulation at the skull base (SBS) results in contraction of limb muscles bilaterally (Ugawa et al., 1991b). Collision experiments and studies in patients with pyramidal signs indicate that SBS activates the corticospinal tract at the cervico-medullary junction (Ugawa et al., 1991b; Ugawa et al., 1992). In the collision experiment, FDI responses after TCMS were greatly diminished when SBS preceded TCMS by up to 2 ms or followed TCMS by up to 2 ms. This indicated that SBS activated the same motor pathway as TCMS which is the corticospinal pathway. This was confirmed in patients with supratentorial lesions and, "clinical pyramidal signs", who had abnormally high SBS thresholds (Ugawa et al., 1992). The abnormally high SBS threshold for muscle activation in these patients was presumed to be due to degeneration within corticospinal pathways which reduced the population of corticospinal fibres available for activation by SBS (including some low threshold fibres). The problem with both the collision experiment and the study in patients with pyramidal signs is that only muscles known to receive strong corticospinal projections were studied.

In Chapter 3, it was determined that the pattern of muscle activation after SBS was different than that after TCMS. Triceps (a muscle known to receive weak

corticospinal excitation) was recruited by SBS before FDI (a muscle known to receive strong corticospinal excitation) in all subjects, indicating the relative strength of projections to spinal motoneurons supplying triceps was greater after SBS than after TCMS.

The different pattern of muscle activation after SBS compared to TCMS in awake subjects may be reflected in different SCEPs after SBS and TCMS. For example, the SCEPs recorded directly from the spinal cord after SBS in anaesthetized patients undergoing spinal operations contained one wave (Rothwell et al., 1994b) while those after TCMS contained multiple waves (Ingherelli et al., 1989; Burke et al., 1993). Unfortunately, SCEPs and the muscle responses after TCMS in anaesthetized patients do not accurately reflect what happens after TCMS in the awake state because anaesthesia either reduces the efficacy of synaptic connections within the brain necessary for indirect activation of corticospinal neurons, or hyperpolarizes cells which, in turn, result in diminished SCEP waves (Matsumura et al., 1988; Baker et al., 1994; Yamada et al., 1994).

In previously reported intraoperative studies, SCEPs were recorded from epidural recording electrodes positioned above and below the operative site after the patient was anaesthetized (Burke et al., 1993). No previous studies have recorded SCEPs (directly from the spinal cord) concomitantly with muscle

responses after SBS in awake human subjects probably because of the invasive nature of the spinal cord recording electrodes. We have overcome this problem by recording SCEPs in subjects with dorsal column stimulating (DCS) electrodes already implanted for pain control. The morphology of the SCEP waveform and its relationship to leg muscle responses in awake subjects may help elucidate the neural structures excited by SBS as well as the SCEP waveform characteristics necessary for activation of leg muscles. This chapter will characterize the SCEP after SBS in awake and anaesthetized conditions. In the following chapter, the SCEP after TCMS will be characterized and compared to the SCEP after SBS in the same subjects.

Methods

Patient Population

Only patients with normal motor and sensory examinations, as determined by the attending physician, were included in the study. Experiments were performed on six subjects (3 male) aged 31 - 62 years (mean 49 years) who underwent surgery for DCS implantation to control pain resulting from arachnoiditis following lower back surgery (three subjects), failed back syndrome (two subjects) and prostatitis (one subject). Two other subjects were

excluded from the study because they had numbness and weakness in the legs.

Analgesic medication was stopped several hours prior to the experiment and no analgesics were given during the experiments. All experimental methods described below were approved by the Research Ethics Board at Sunnybrook Health Science Centre and all patients gave their informed consent to participate in the experiments.

Stimulating Techniques

SBS procedures were the same as those described in the previous Chapter 2. The stimulus intensity was initially set at 10% of the maximum output of the stimulator and then adjusted in two percent increments until a reproducible SCEP was obtained with minimal stimulus intensity (T). The stimulus intensity was increased by 7.5% increments (7.5% maximum output of the stimulator) to T + 22.5% in three steps.

Recording Techniques

SCEP recordings were obtained from the DCS electrode (Medtronic Neurological, Model 3586 or 3986, Minneapolis, USA) according to the methods described in Chapter 2. For recording purposes, the two phone jack tips were connected to G1 (DCS electrode one) and G2 (DCS electrode three) of a differential amplifier (Cadwell Laboratories Inc., Kennewick, WA, USA).

CMAPs were recorded from cup disc electrodes (1 cm diameter) placed 3 cm apart on the skin overlying the muscle belly of the left biceps, triceps, FDI, TA and Sol in all subjects in the manner described in Chapter 2.

The SCEP and muscle responses were recorded simultaneously on an eight channel evoked potential machine (Cadwell Excel, Cadwell Laboratories Inc., Kennewick, WA). The amplifier gain was initially set at 50 μV per division for SCEP and 100 μV per division for muscle recordings. The recording bandpass was 30 - 5000 Hz for muscle and SCEP recordings. Sweep duration was usually 70 ms and the time base was shortened after data acquisition for accurate measurement of SCEP peaks.

SCEP Conduction Velocity:

The onset latency of the SCEP was divided into the distance from the inion

(level of anode and cathode) to the Th7 spinous process (level of DCS electrode) for each subject. The Th7 spinous process overlies the body of Th8 where the DCS electrode was positioned.

Facilitation Studies

Three of the six subjects participated in the facilitation experiment. Recordings were obtained at rest and during voluntary activation of triceps using a SBS intensity of T + 7.5%. Recordings were obtained at rest and during voluntary activation of TA using a SBS intensity of T + 22.5%. Voluntary activation of TA or triceps was maintained at 10% maximum voluntary contraction as measured by an EMG biofeedback machine as described in Chapter 2. SBS was delivered shortly after 10% maximum voluntary triceps or TA contraction was achieved. Trials were obtained during rest and muscle activation in an alternating fashion. To ensure that only triceps or TA was activated, relaxation of the other muscles was monitored by a live EMG display and an EMG audio monitor of each channel on the Cadwell Excel evoked potential machine.

Intraoperative Studies

Two of the six subjects had SBS studies repeated while under general anaesthetic for surgical internalization of the DCS apparatus two or three days after the completion of experiments described above. Stimulating and recording procedures for the SCEP were the same as those described in the awake study except only one stimulus intensity was used (T + 22.5%) due to intraoperative time constraints. Anaesthesia was induced with 250 µg fentanyl, 10 mg atracurium, 400 mg pentothal, 140 mg succinylcholine and maintained using inhalation agents (0.5% isoflurane, 66% N_2O and 33% O_2 in both subjects). Muscle responses were not studied.

Data Analysis

The amplitude, latency, duration and rectified area of the SCEP was measured as described in Chapter 2. The onset latency and peak-to-peak amplitude of all muscle responses was measured from the average of the first two responses after SBS.

Results

Skull Base Stimulation At Rest

The minimum intensity for activation of reproducible SCEPs after SBS ranged from 20 to 35% maximum output of the stimulator (mean = 23%) when the six subjects were at rest. The SCEP had one negative peak at all stimulus intensities in all subjects (Fig. 1). Mean SCEP amplitude, latency and duration at T + 22.5% are shown in Table 1. The SCEP amplitude greatly increased as stimulus intensity increased. In contrast, the SCEP latency did not greatly change in each subject as SBS intensity increased (Fig. 2). At SBS T + 22.5%, the fastest conducting fibres contributing to the SCEP had a mean conduction velocity of 94 m/sec (SD = 10.4 m/sec, range = 80 - 103 m/sec) calculated by the distance from the inion to the spinous process of Th7 ÷ SCEP onset latency.

SBS evoked responses from the biceps, triceps and FDI in all subjects but failed to activate the TA at the highest stimulus intensity (T + 22.5%) in three of the six subjects. When the responses were present in the lower extremity, they had a very low amplitude relative to the upper extremity responses across all stimulus intensities. These results corroborated the findings in Chapter 3.

Stimulus current spread to nerve roots was suspected when the onset latency of a muscle response from the upper extremity decreased in a step-like fashion without a decrease in SCEP latency as SBS intensity increased. Stimulus

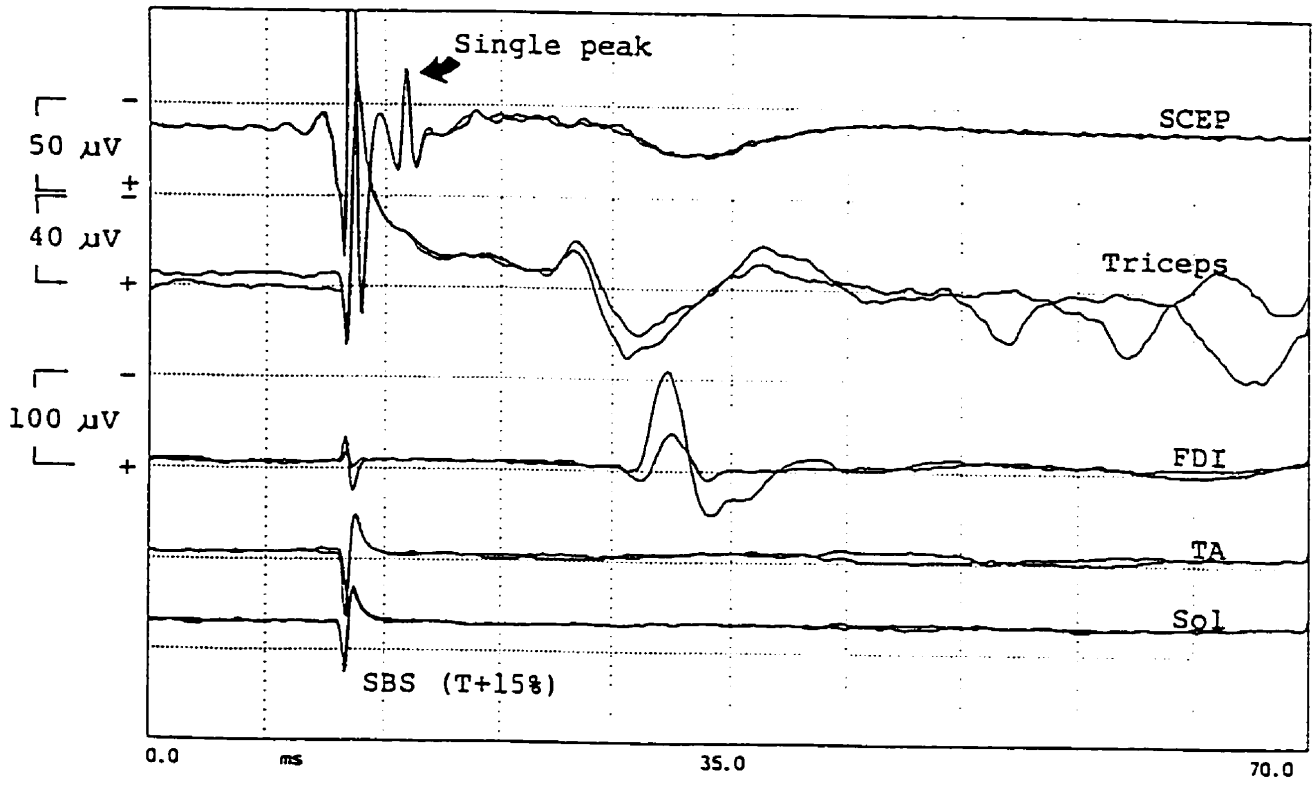


Figure 1. A spinal cord evoked potential (SCEP) recorded from an epidural electrode at Th8, and muscle responses recorded from the left biceps, triceps, first dorsal interosseous (FDI), tibialis anterior (TA) and soleus (Sol) after percutaneous electrical stimulation at the skull base (SBS) in a subject at rest. The SBS intensity was SCEP threshold (T) + 15% of the maximum output of the stimulator. The SCEP was triphasic with a single negative peak. No responses were obtained from TA and Sol. The stimulus pulse was given 11.4 ms after the beginning of the sweep. Each trace consists of 2 superimposed single responses.

TABLE 1.

NORMAL DATA FOR SPINAL CORD EVOKED POTENTIALS RECORDED AT Th8 AFTER PERCUTANEOUS ELECTRICAL STIMULATION AT THE SKULL BASE IN SIX SUBJECTS AT REST

SKULL BASE STIMULATION (T + 22.5%)

		n = 6
Latency (Mean ± SD)	onset [1] (ms)	3.7 ± 0.44
	neg peak (ms)	4.4 ± 0.44

		n = 6
Amplitude (Mean ± SD)	onset - neg peak (μV)	33.9 ± 12.2
	neg - next pos peak (μV)	42.5 ± 9.7

		n = 6
SCEP Duration (Mean ± SD)	onset - last pos peak (ms)	2.2 ± 0.26

[1] *onset* is the initial negative deflection of the wave

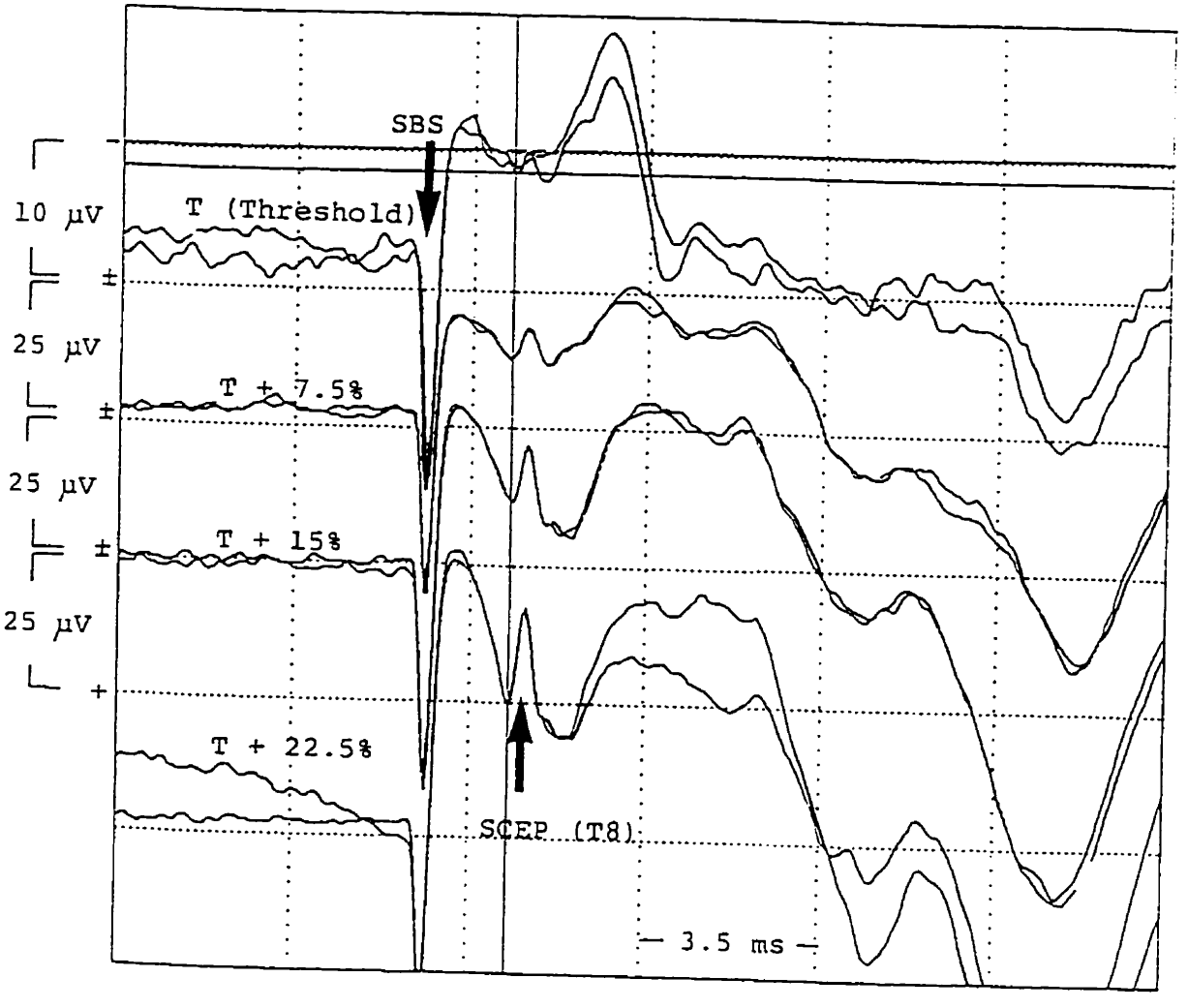


Figure 2. A spinal cord evoked potential (SCEP) recorded from an epidural electrode at Th8 in one subject. The SCEP waveform had a short duration and contained one negative peak at all stimulus intensities. The long duration waveforms following the SCEP likely reflect volume conducted myogenic activity. The SCEP amplitude increased as stimulus intensity increased but the SCEP onset latency did not. Each trace is an average of 3 to 5 responses.

current spread to cervical nerve roots supplying triceps was suspected in three of the six subjects. They had a step-like decrease in triceps onset latency (mean ± SD = 1.95 ± 0.6 ms) when the stimulus intensity increased from T + 15% to T + 22.5%. In contrast, the SCEP onset latency did not significantly decrease (mean ± SD = 0.1 ± 0.1 ms) which verified the suspicion of stimulus current spread to cervical nerve roots and not to more caudal spinal cord structures. The other subjects did not demonstrate a step-like decrease in either muscle response or SCEP latency as SBS intensity increased from T to T + 22.5% in 7.5% increments.

Facilitation Studies

Voluntary Activation of Triceps: During rest, the SCEP after SBS T + 7.5% contained one wave and muscle responses were obtained from biceps and triceps in all three subjects who participated in the facilitation experiment. No responses were obtained from FDI in two of the three subjects and from TA and Sol in all three subjects at rest. Voluntary activation of the triceps increased the amplitude of the triceps and biceps responses in all subjects (Biceps (mean ± SD): 12.7 ± 5.8 μV to 65.3 ± 27 μV; Triceps: 23 ± 16.7 μV to 279.3 ± 258 μV) and decreased the latency of triceps in all subjects and biceps in two of three subjects (Biceps (mean±SD): 0.9 ± 0.8 ms, range 0 - 1.6 ms;

Triceps: 1.7 ± 1.2 ms, range 0.3 - 2.5) (Fig. 3). Voluntary activation of triceps at SBS T + 7.5% did not facilitate muscle responses from TA and Sol.

One of the two subjects with absent FDI responses at rest had a small FDI response during triceps activation but the other subject did not. The subject with FDI present during rest had no change in the FDI response during voluntary activation of triceps.

Voluntary Activation of TA: At T + 22.5%, the SCEP contained one wave and muscle responses were obtained from biceps, triceps and FDI in all three subjects and from TA and Sol in one of the three subjects at rest. Voluntary activation of TA facilitated muscle responses in the upper and lower extremities. The two subjects who had absent TA and Sol responses during rest had present responses during voluntary activation of TA (Fig. 4). In contrast, the SCEP rectified area and latency did not significantly change (SCEP rectified area: paired *t* test, T = 1.36, p = 0.8; SCEP latency: no change in all three subjects). The amplitude (mean ± SD) of the TA response during rest and during voluntary activation of TA was 1.9 ± 3.2 μV (range = 0 - 5.6 μV) and 393 ± 166 μV (range = 260 - 580 μV) respectively. The subject that had a present TA response during rest had TA latency decrease from 38.2 ms to 27.1 ms and the amplitude increase from 5.6 μV to 580 μV.

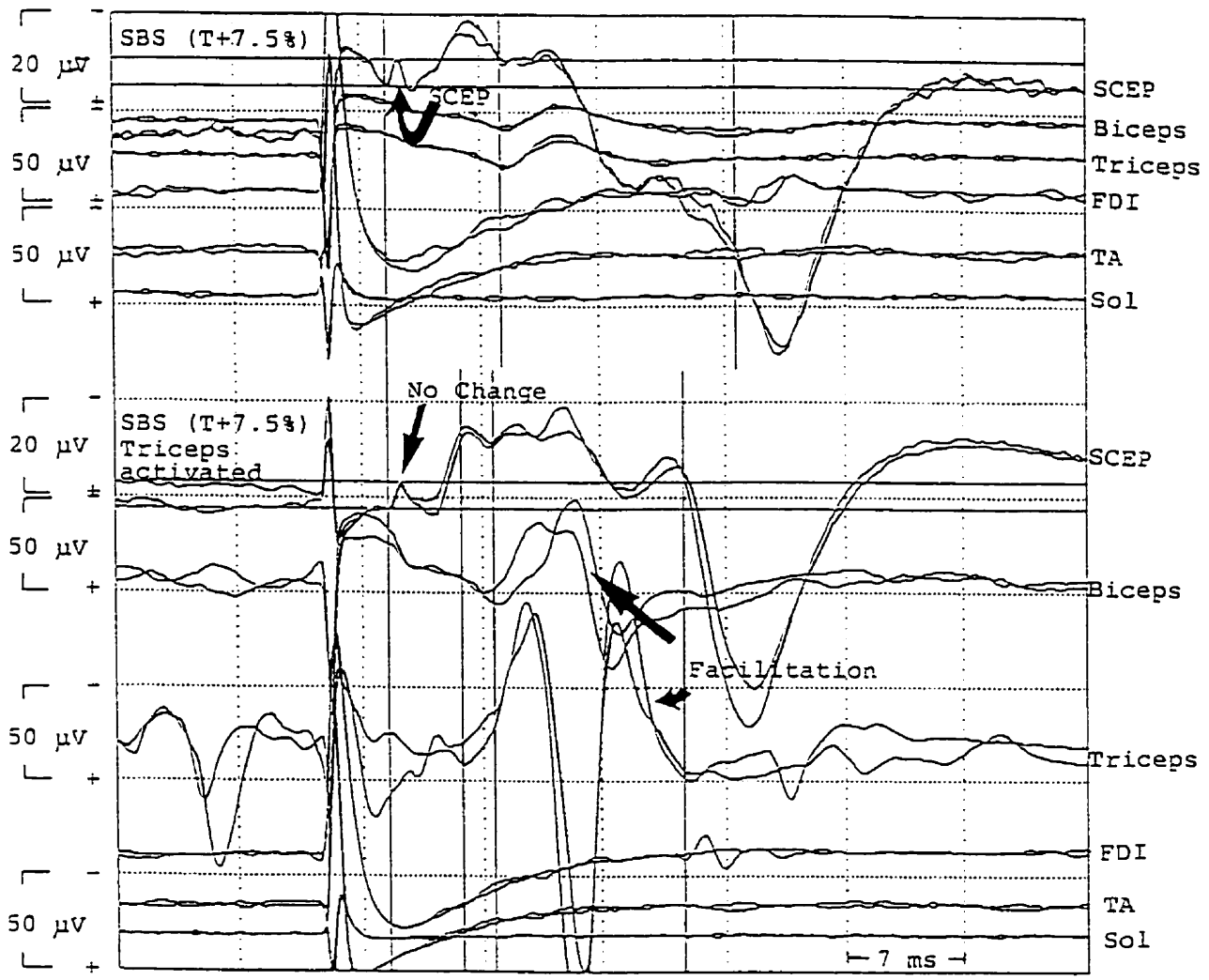


Figure 3. The effect of voluntary activation (10% of maximum voluntary contraction) of triceps on the spinal cord evoked potential (SCEP) and muscle responses after percutaneous electrical stimulation at the skull base (SBS) using a stimulus intensity of SCEP threshold (T) + 7.5% maximum output of the stimulator in one subject. The SCEP was recorded from an epidural electrode at Th8. The top six traces were obtained at rest and the bottom six traces were obtained during voluntary activation of triceps. There was facilitation of the biceps and triceps muscle responses but no change in the onset-to-peak SCEP amplitude (6.0 µV) during voluntary activation of triceps compared with that obtained at rest when the same stimulus intensity was used.

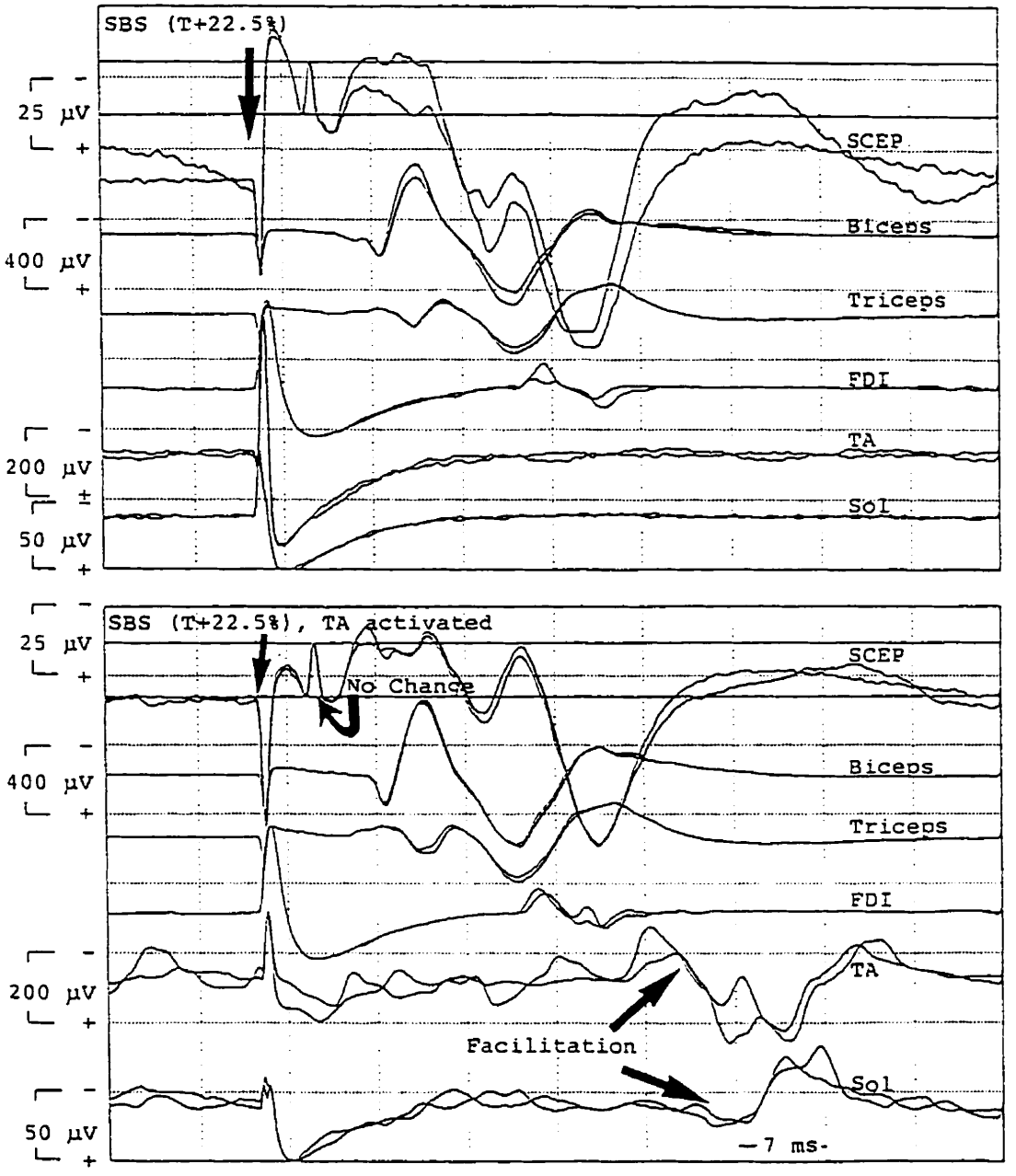


Figure 4. The effect of voluntary activation (10% of maximum voluntary contraction) of tibialis anterior (TA) on the spinal cord evoked potential (SCEP) and muscle responses after percutaneous electrical stimulation at the skull base (SBS) using a stimulus intensity of SCEP threshold (T) + 22.5% maximum output of the stimulator in one subject. The SCEP was recorded from an epidural electrode at Th8. The top six traces were obtained at rest and the bottom six traces were obtained during voluntary activation of TA. Facilitation was greatest in soleus (Sol) and TA during voluntary activation of TA. In contrast, there was no change in the onset-to-peak SCEP amplitude (18.1 µV) compared with that obtained at rest when the same stimulus intensity was used.

Intraoperative Study:

The SCEP rectified area and latency did not greatly change during general anaesthesia in the two subjects who participated in the intraoperative study. The SCEP onset latency increased from 4.1 to 4.4 ms in one subject and 3.4 - 3.8 ms in other. The onset-peak amplitude decreased from 23 μV to 18 μV in one subject and from 48 μV to 43 μV in the other but the triphasic nature of the SCEP wave did not change after the subject was on inhalation anaesthetic. Temperature of both patients during intraoperative recordings was 36.1 and 36.2∘C respectively. It was possible that these small changes in SCEP amplitude and latency were related to a change in the position of the DCS recording electrode on the spinal cord after the patient was positioned prone on the operating table.

Discussion

We have characterized the SCEP after SBS in six awake human subjects. We have demonstrated that descending SCEPs after SBS can be reliably recorded from an epidural electrode positioned over the dorsal columns at Th8 in awake human subjects. Artifacts related to background EMG and evoked muscle

activity were minimized by recording from closely spaced epidural electrodes (2 cm apart).

The SCEP after SBS had a short latency with one negative peak. The fastest conducting fibres contributing to the SCEP had a conduction velocity between 80 and 103 m/sec (mean = 94) which was faster than that estimated in Chapter 3 using F responses to FDI and TA (mean = 75 m/sec and 68 m/sec respectively). The technique used in this chapter is likely to be a more accurate estimate of conduction velocity because there are fewer variables in the equation. Nevertheless, the distance from the inion to the Th7 spinous process used in the calculation of conduction velocity only approximated the real distance between the site of activation and the DCS electrode (G1) so there are inherent problems with both techniques. The mean conduction velocity of 94 m/sec is consistent with conduction velocities reported in animal studies for corticospinal fibres (12 - 100 m/sec) and non-corticospinal fibres (reticulospinal, vestibulospinal and rubrospinal; 31 - 150 m/sec), but is out of the range of conduction velocity reported for dorsal column fibres (< 70 m/sec) (Woolsey and Chang, 1948; Patton and Amassian, 1954; Lund and Pompeiano, 1965; Eccles et al., 1974, Bantli et al., 1975; Bloedel and Bantli, 1978; Brodal, 1981; Levy, 1983; Levy et al., 1986). The overlap of conduction velocity in corticospinal and non-corticospinal fibres, and the inherent errors associated with conduction velocity estimates, makes it difficult to discriminate the pathway

that mediated a response based on conduction velocity alone. In human studies, it is difficult to obtain conduction velocity from only one tract because the stimulating and recording electrodes are necessarily less invasive and therefore less discrete.

Percutaneous electrical stimulation is not a discrete stimulation technique because the anode and cathode are separated by at least 10 cm and the stimulus voltage necessary for activation of muscles is high (> 150 V). Consequently, antidromic and orthodromic activation of many fast conducting long tracts traversing the brainstem may have occurred. Collision studies have shown that low intensity SBS activates at least corticospinal axons, probably at the pyramidal decussation (Ugawa et al., 1991b; Rothwell et al, 1994b).

High intensity SBS can activate cervical nerve roots (see Chapter 3, Fig. 6; Ugawa et al., 1991b; Rothwell et al., 1994). In this experiment, stimulus current spread to nerve roots was suspected when an increase in stimulus intensity caused a step-like decrease in triceps response amplitude without a concomitant decrease in SCEP amplitude. This occurred in three of six subjects when the SBS intensity was T + 22.5 %. Triceps activation during SBS (T + 7.5%) facilitated the triceps response which verified that low intensity SBS activated long tracts (not nerve roots) that connected to motoneurons with increased excitability. The shorter triceps latency and larger triceps amplitude

observed during facilitation was likely caused by earlier depolarization of a larger number of alpha motoneurons. Stimulus current spread to structures located more caudally in the spinal cord was not suspected because the SCEP latency did not greatly change as SBS intensity increased. While the SCEP recorded from Th8 does not reflect activity in pathways that activate triceps, it is expected that stimulus current spread would affect the latency of the SCEP regardless of the recording site.

The SCEP we recorded from Th8 was suitable for detecting changes in neural outflow to the lower extremity and trunk. Voluntary muscle contraction of TA facilitated all muscle responses without changing the SCEP rectified area or latency. This suggests that SBS directly excited long fibre tracts in the medulla or high spinal cord, not central nervous system structures that could be influenced by changes in synaptic input. Accordingly, it is likely that the excitability of spinal motoneurons at multi-segmental levels is increased to account for the facilitation of muscle responses.

The mechanisms responsible for facilitation are poorly understood. Previous investigators (Delwaide and Toulouse, 1981; Pereon, et al., 1995) have proposed two distinct mechanisms to explain this phenomenon; 1) moderate motor facilitation from a supraspinal origin, and 2) a more marked facilitation resulting from proprioceptive afferent impulses originating from the target

muscle contraction (TA) that are transmitted to supraspinal relays (yet unknown) and then descend in facilitatory pathways. It is also possible that spinal motoneuron excitability at multi-segmental levels was increased because of activation of muscles other than the TA despite our best efforts to ensure they were relaxed.

SBS intensities up to T + 22.5% produced low amplitude leg muscle responses in only half of the subjects at rest. In chapter 3 it was demonstrated that high SBS (T + 37.5%) could activate responses from leg muscles in seven of eight subjects but the amplitude of these responses are small compared to those reported after TCMS (Terao et al., 1994). The SCEP we recorded after SBS consisted of a single descending volley while that after TCMS and TCES in monkeys and anaesthetized humans contains multiple descending volleys (D and I waves) that may more effectively depolarize motoneurons and interneurons in the lumbo-sacral spinal cord by bringing their membrane potential to threshold by summation. The opportunity for a summation effect on motoneurons in the lumbo-sacral spinal cord was reduced after SBS because the SCEP contained only one volley.

The summation effect of SCEP waves is important for activation of alpha motoneurons. For example, muscle responses after TCMS and TCES are absent or significantly diminished in patients under anaesthesia and this is

related to absent or diminished SCEP I waves (Burke et al., 1990; Burke et al., 1992). Motor cortex stimulation studies (Taniguchi et al., 1993) have shown that if the I waves are artificially recreated by direct brain stimulation using a train of five square wave stimulus pulses separated by one or two milliseconds then muscle responses are activated.

The latency of the SCEP after SBS (T + 22.5%) minimally increased and the amplitude minimally decreased when the subjects were under general anaesthetic. This likely due to either patient cooling which slowed the conduction velocity and caused a small amount of temporal dispersion in fibres contributing to the SCEP or a change in the position of the DCS recording electrode on the spinal cord after the patient was positioned prone on the operating table. The SCEP after SBS had a short latency and was robust in subjects under general anaesthesia suggesting it is not dependent on synaptic transmission and likely results from activation of long tracts in the distal brainstem or high spinal cord.

In summary, the SCEP after SBS contained one wave that had a fast conduction velocity. SBS activated central motor pathways that preferentially excited alpha motoneuron pools supplying triceps and biceps. Voluntary activation of TA during SBS facilitated muscle responses from both upper and lower extremities (lower extremities more than upper extremities) without

changing the descending SCEP. The SCEP after SBS was not greatly affected by general anaesthesia indicating the SCEP after SBS was not dependent on synaptic transmission.

CHAPTER VI

Spinal Cord Evoked Potentials And Muscle Responses Recorded Directly From The Spinal Cord After TCMS In Awake Human Subjects

Abstract

The neural structures excited by transcranial magnetic stimulation (TCMS) were determined by recording spinal cord evoked potentials (SCEPs) from dorsal column stimulating (DCS) electrodes in ten awake, neurologically intact human subjects. Muscle recordings were concomitantly recorded from the left biceps, triceps, first dorsal interosseous, quadriceps, tibialis anterior (TA) and soleus (Sol) while the subjects were at rest. The magnetic stimulator coil was positioned for optimal activation of the left TA. Threshold (T) for activation of the SCEP varied between 40 and 60% of the maximum output of the stimulator. In three subjects, the D wave (direct activation of corticospinal neurons) and the first I wave (I_1, indirect activation of corticospinal neurons) of the SCEP were recruited simultaneously, in one subject the D, I_1 and I_2 waves were recruited simultaneously and in another subject the I_1, I_2 and I_3 waves were recruited simultaneously. In the remaining five subjects, only the I_1 wave was recruited first. The stimulus intensity was increased by 10% increments (10% of the maximum output of the stimulator) to T + 30% in three steps. Increasing the stimulus intensity to T + 10% recruited the D wave in nine of the ten subjects. The I_2 and I_3 waves were present at T + 10% (5/10 subjects), T + 20% (9/10 subjects) or T + 30% (10/10 subjects). Usually, the leg muscle responses (TA and Sol) were contingent on the SCEP containing at least four waves (D, I_1, I_2, I_3). T + 30% produced a SCEP with five waves (D, I_1, I_2, I_3, I_4) in five subjects,

four waves in the other five subjects (absent I_4) and muscle responses from the lower extremities in eight of the ten subjects. The rectified SCEP area and amplitude of the D and I waves increased with increasing stimulus intensity but the latencies of the D and I waves did not greatly change. The spinal cord conduction velocity measured between two electrodes at Th8 was 83 m/sec in one subject and 61 m/sec in another.

No previous studies have recorded D and I waves from awake human subjects. This technique may be important for assessing the excitatory and inhibitory influences on corticospinal neurons in the sensorimotor cortex during the planning and execution of motor tasks in humans. Our results may have clinical importance for determining the optimum way of activating corticospinal pathways for intraoperative monitoring of motor pathways.

Introduction

Transcranial magnetic stimulation (TCMS) in anaesthetized humans and sub-human primates evokes a descending spinal cord evoked potential (SCEP) that contains a D wave followed by several I waves (Amassian et al., 1990; Edgley et al., 1990; Thompson et al., 1991; Burke et al., 1993; Kitigawa and Moller, 1994). The D wave is thought to result from direct activation of corticospinal neurons (probably at the initial segment) and the I waves are thought to result from indirect activation of corticospinal neurons via interneurons excited by the stimulus (Patton and Amassian 1954; Amassian et al., 1990; Berardelli et al., 1991; Edgley et al., 1990) but their is recent evidence to suggest the D wave is results from activation of corticospinal fibres at their bends when a coil orientation that induces a latero-medial electrical field is used (Amassian et al., 1992). The D and I waves are thought to descend in the corticospinal tracts and generate a sequence of EPSPs at the spinal motoneurons causing them to fire by temporal summation (Mills, 1991; Taylor et al., 1993). If the spinal motoneuron potential is already near threshold then it is more likely that an earlier wave in the SCEP will cause it to fire (Day et al, 1987; Mills, 1991).

The effect of D and I waves on muscle responses after TCMS have been estimated in awake humans using peri-stimulus-time histograms (PSTHs) of motor unit firing (Day et al., 1989; Priori et al. 1993; Awiszus and Feistner,

1994). These studies have estimated that spinal motoneurons supplying hand muscles receive only I waves (Day et al., 1989) while spinal motoneurons supplying tibial anterior (TA) receive D and I waves (Priori et al., 1993; Awiszus and Feistner, 1994) These conclusions are not based on actual D and I wave recordings but rather on the effect that D and I waves may have on individual motoneurons.

To date, the neural elements excited by TCMS have been deduced from muscle recordings in awake humans (Day et al., 1989), SCEPs in anaesthetized humans (Berardelli et al., 1991; Burke et al., 1993), SCEPs in anaesthetized sub-human primates (Amassian et al., 1990; Edgley et al 1990) and SCEPs in one awake sub-human primate (Baker et al., 1994, Baker et al., 1995). In the awake sub-human primate, a D wave was present but the I waves were either absent or small probably because the recording electrodes were too close together. This resulted in phase cancellation of the I waves (Baker et al., 1994).

No previous studies have recorded D and I waves directly from the spinal cord after TCMS in awake humans so it is still not clear which elements of the human brain are excited by TCMS and what waves are necessary for activation of leg muscles. We have recorded D and I waves directly from the spinal cord after TCMS in human subjects who were awake and later anaesthetized. We

have shown that TCMS can directly and indirectly activate corticospinal neurons in the awake human and that the leg muscle responses during rest are dependent on multiple SCEP waves.

Methods

Patient Population:

Experiments were performed on ten subjects (7 male) aged 31 - 62 years (mean 49 years) who underwent surgery for DCS implantation to control pain resulting from arachnoiditis following lower back surgery (three subjects), failed back syndrome (six subjects) and prostatitis (one subject). Analgesic medication was stopped several hours prior to the experiment and no analgesics were given during the experiments. All patients had normal motor and sensory examinations. Six of the ten subjects participated in the previous SBS experiment. Two other subjects were excluded from the study because of leg numbness and weakness.

Surgical Implantation Of The Dorsal Column Stimulating Electrode:

The procedure for surgical implantation of the DCS electrode was described in the Chapter 2.

Transcranial Magnetic Stimulation:

The brain was stimulated by a Novametrix (Novametrix Medical Systems Inc., USA) Magstim Model 200 and a standard circular coil (internal diameter of coil was 5.4 cm, outer diameter was 11.6 cm) as described in Chapter 2. The coil was held tangential to the scalp with current flowing in the coil in a clockwise direction (B side of the stimulator up). The coil position that resulted in maximum activation of left TA with minimum stimulus intensity during rest was determined as described in Chapter 2. This stimulus intensity was termed "threshold" (T). The stimulus intensity was increased by 10% increments (10% maximum output of the stimulator) to T + 30% in 3 steps. The stimulus was given 9.73 ms after the onset of the sweep.

Recording Techniques:

SCEP recordings were obtained from the same DCS electrode used in the previous study. In two subjects, the SCEP was also recorded from DCS electrode one (G1) - skin surface at Th8 (G2), and DCS electrode three (G1) - skin surface at Th8 (G2). The surface electrode at Th8 was a Grass cup disc electrode (1 cm diameter) (Grass Instruments, Quincy, Massachusetts, USA). The conduction velocity of the SCEP was calculated by dividing the distance between the two electrodes on the spinal cord (2 cm) by the difference in

latency between the two SCEP waveforms recorded from each site.

The procedure for recording CMAPs was described in Chapter 2. Recordings were obtained from left biceps, triceps, first dorsal interosseous (FDI), quadriceps, tibialis anterior (TA) and soleus (Sol) in all subjects.

The SCEP and muscle responses were recorded simultaneously on an eight channel evoked potential machine (Cadwell Excel, Cadwell Laboratories Inc., Kennewick, WA) as described in Chapter 2. Sweep duration was 70 ms but the time base was shortened after data acquisition for accurate measurement of SCEP peaks.

Intraoperative Studies:

TCMS studies were repeated in three of the ten subjects during surgery for internalization of the DCS apparatus. After induction of aesthesia, inhalation agents (0.5% - 1.0% isoflurane, 55-66% N_2O, and O_2) were used to maintain a constant level of aesthesia in all three subjects. Experiments were performed after the patients were on inhalation agents. Recording variables and position of the stimulating coil were the same as those described above. The TCMS intensity was T + 40% in all three subjects.

Data Analysis:

The method for analyzing SCEP waves was described in Chapter 2. If the SCEP had more than one wave then the interwave latency was calculated between the wave onsets (initial negative deflection) and between the negative peaks of each wave. For each muscle response, the onset latency and peak-to-peak amplitude were measured from the average of two responses as previously described. Typically, the muscle recordings were obtained at the beginning of each SCEP average.

The SCEP rectified area, duration and maximum peak-to-peak amplitude after TCMS were statistically compared to those after SBS at each stimulus intensity using paired *t* tests in the six subjects who participated in both SBS and TCMS experiments. Measures obtained after TCMS T were compared to those obtained at SBS T, measures obtained after TCMS T + 10% were compared to those after SBS T + 7.5%, measures obtained at TCMS T + 20% were compared to those after SBS T + 15% and measures obtained after TCMS T + 30% were compared to those after SBS T + 22.5%.

Results

The mean optimal stimulator coil position for activation of left TA was 4 ± 0.7 cm anterior to Cz (International 10 - 20 system) and 1.6 ± 0.7 cm to the left of Cz. Stimulus intensity necessary for activation of TA during rest varied from 50% to 100% of the maximum output of the stimulator (mean = 69 ± 18).

T for activation of the SCEP varied between 40% and 60% maximum output of the stimulator (mean = 49 ± 7.5). In three subjects, the D wave (direct activation of corticospinal neurons) and the first I wave (I_1, indirect activation of pyramidal neurons) of the SCEP were recruited simultaneously. In one subject the D, I_1 and I_2 waves were recruited simultaneously and in another subject the I_1, I_2 and I_3 waves were recruited simultaneously. In the remaining five subjects, only the I_1 wave was recruited first. Increasing the stimulus intensity to T + 10% recruited the D wave in all subjects but one. At T + 10%, the I_1 wave amplitude (onset-to-peak) was greater than the D wave amplitude in seven subjects (one subject did not have a D wave), equal to the D wave amplitude in two subjects and less than the D wave amplitude in one subject. The pattern of D and I wave recruitment for one subject is shown in figure 1. The order of activation of D and I waves for all subjects is shown in figure 2. The effect of TCMS intensity on the mean amplitude of each wave at each

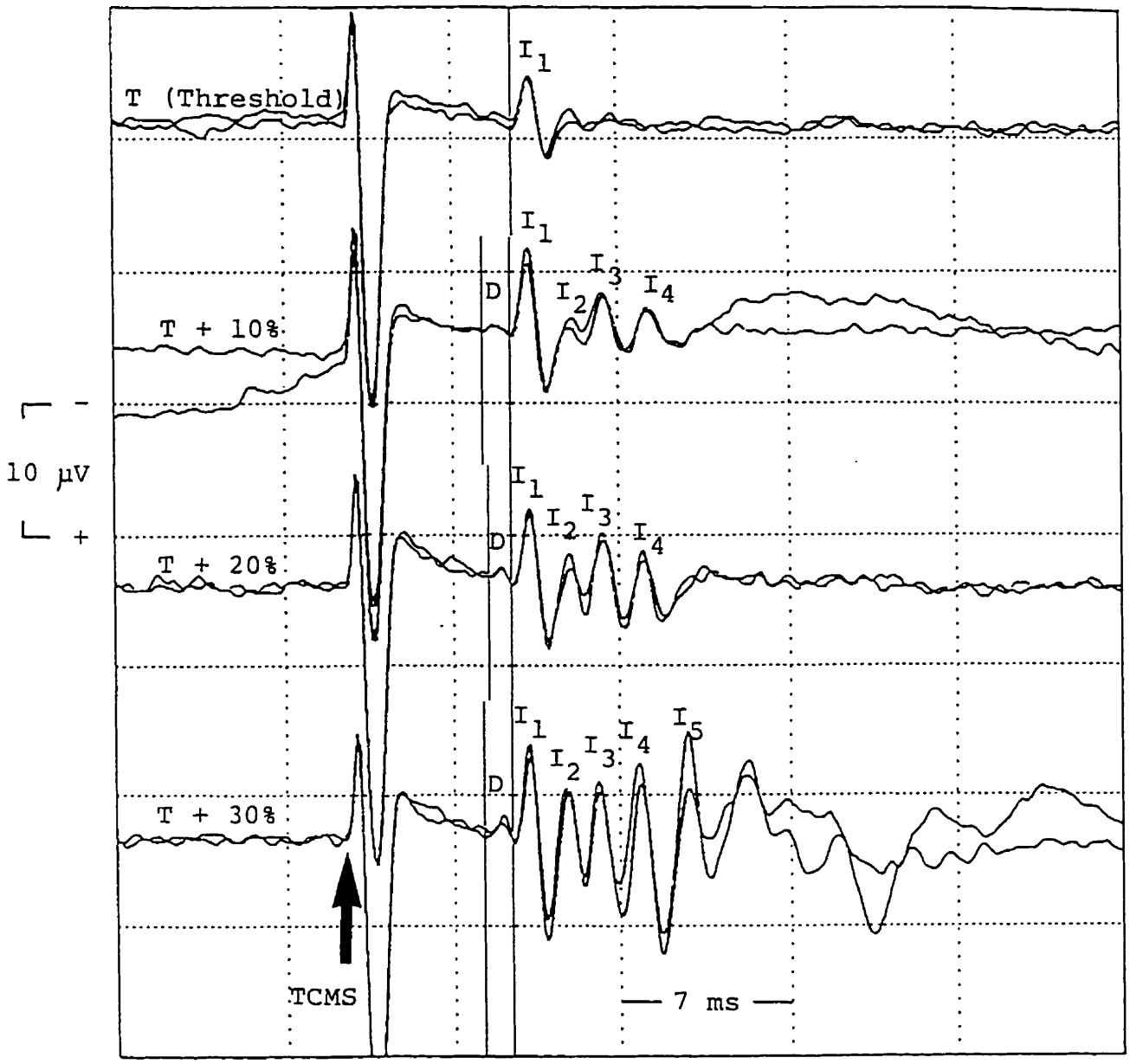


Figure 1: The pattern of activation of D and I waves recorded from an epidural electrode at Th8 after transcranial magnetic stimulation (TCMS) in one subject. The stimulating coil was positioned for optimal activation of left tibialis anterior. The stimulus intensity was adjusted until only a liminal but reproducible spinal cord evoked potential (SCEP) could be recorded. This stimulus intensity was termed threshold (T). Only the I_1 wave was recruited at T. The stimulus intensity was increased by 10% increments (10% of the maximum output of the stimulator) to T + 30% in three steps. The amplitude (but not latency) of each wave contained in the SCEP (D, I_1, I_2, I_3, I_4) greatly increased and more waves were recruited as stimulus intensity increased. Each trace is an average of 5 responses. Two traces were superimposed for waveform reproducibility.

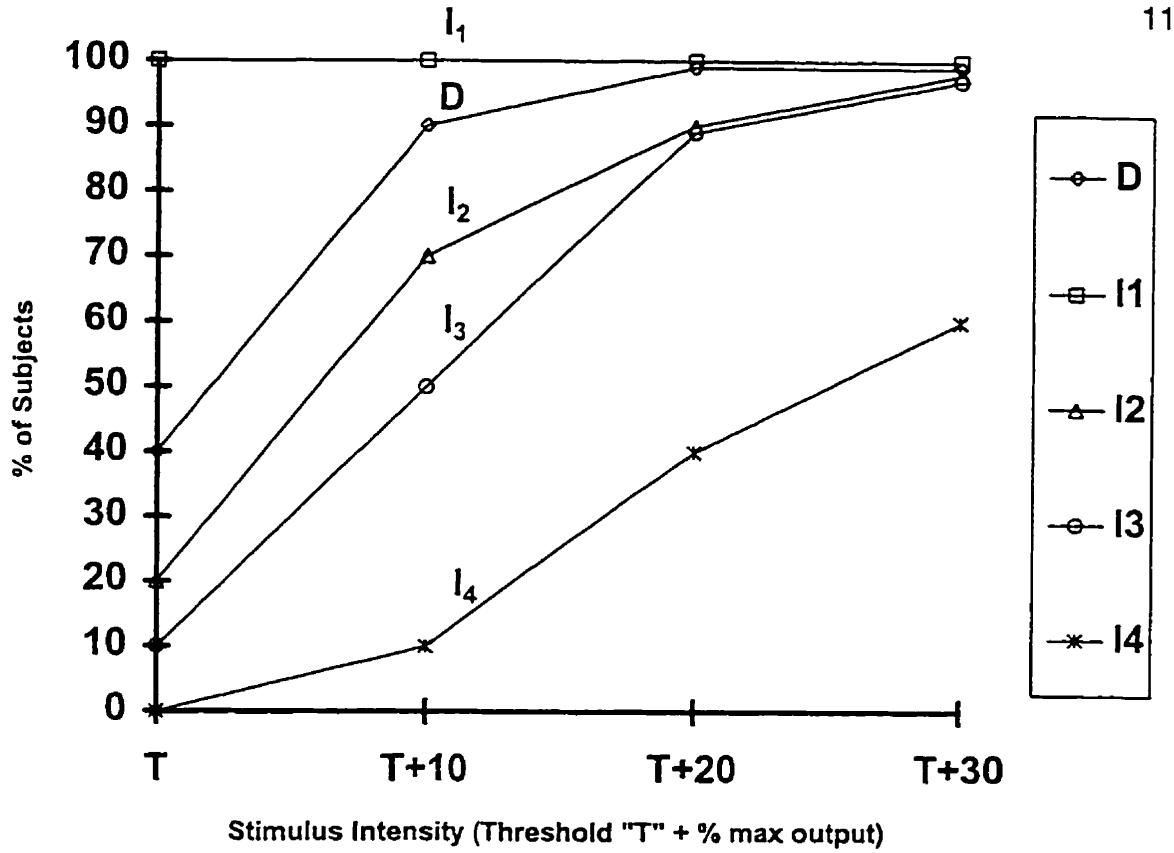


Figure 2. Order of activation of D and I waves after TCMS in 10 control subjects. Threshold (T) was the minimum intensity necessary to elicit a reproducible spinal cord evoked response recorded from an epidural electrode at Th8. I_1 was recruited at T in all subjects but the D wave was recruited at T in only 40% of subjects. More waves were recruited as TCMS intensity increased.

stimulus intensity is shown in figure 3.

The I_2 and I_3 waves were present at T + 10% (5/10 subjects), T + 20% (9/10 subjects) or T + 30% (10/10 subjects). The TA and Sol muscle responses were contingent on the presence of at least four SCEP waves (D, I_1, I_2 and I_3) in all subjects except two. These 2 subjects did not have a TA response at T + 30% at rest despite having a SCEP that contained four waves. One subject had very low amplitude I_2 and I_3 waves. The TCMS intensity was increased to T + 40% in these subjects and activated another I wave (I_5) in one subject, increased the amplitude of I_2 and I_3 in the other subject and evoked a TA response in both subjects.

SCEP and muscle responses data was complete for all subjects at all stimulus intensities up to T + 30%. T + 30% produced a SCEP with five waves (D, I_1, I_2, I_3, I_4) in five subjects and a SCEP with four waves in the other five subjects (absent I_4). All subjects had FDI responses at T + 30%.

The absolute SCEP rectified area at a given stimulus intensity was greatly different between subjects (Fig. 4) but when the data was normalized by converting absolute SCEP rectified area values (obtained at each stimulus intensity) into a percentage of the SCEP rectified area obtained at T + 30% the SCEP rectified area increased proportional to stimulus intensity in all subjects.

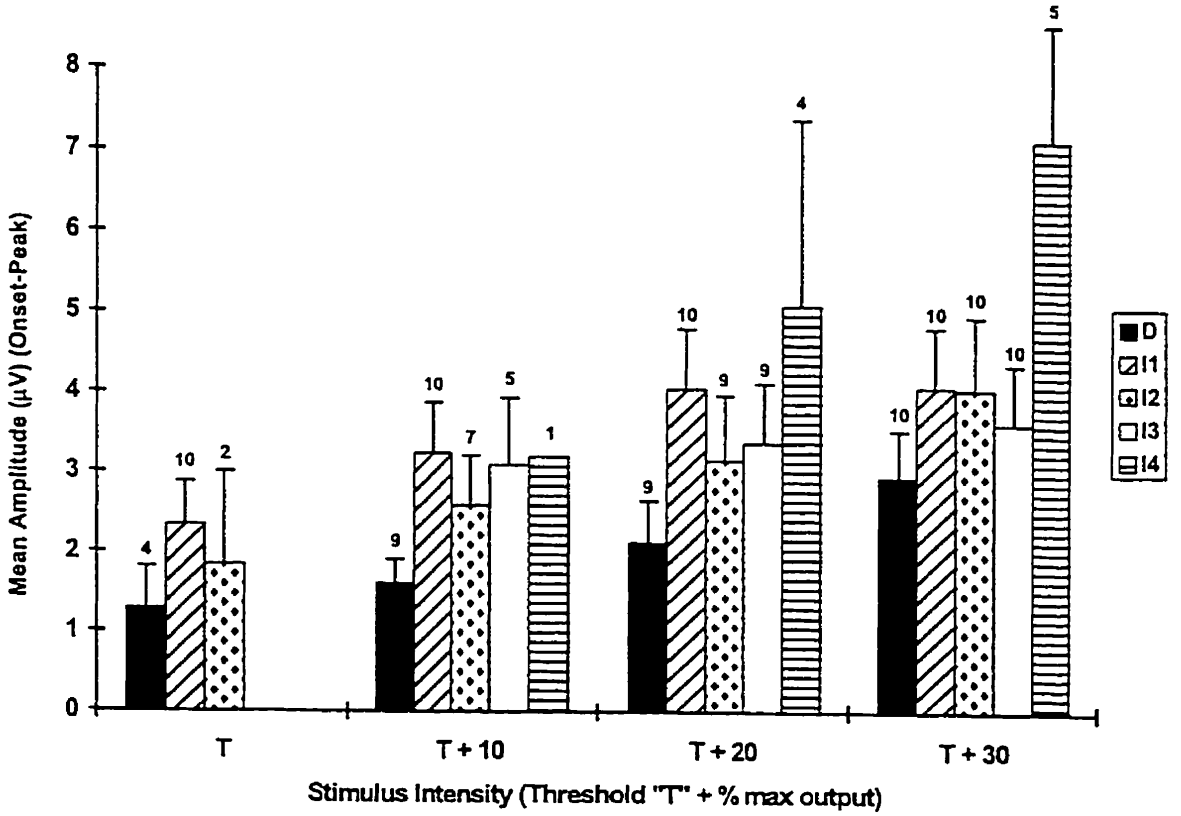


Figure 3: The effect of transcranial magnetic stimulus (TCMS) intensity on the amplitude (onset to negative peak) of the D and I waves recorded from an epidural electrode at Th8. Each bar represents the mean amplitude of each wave and the number above each bar represents the number of subjects in the sample. The I_1 wave was recruited at spinal cord evoked potential threshold (T) in all ten subjects and the D wave was concomitantly recruited with I_1 in four of these. At T + 10% the D wave was recruited in nine of ten subjects.

A.

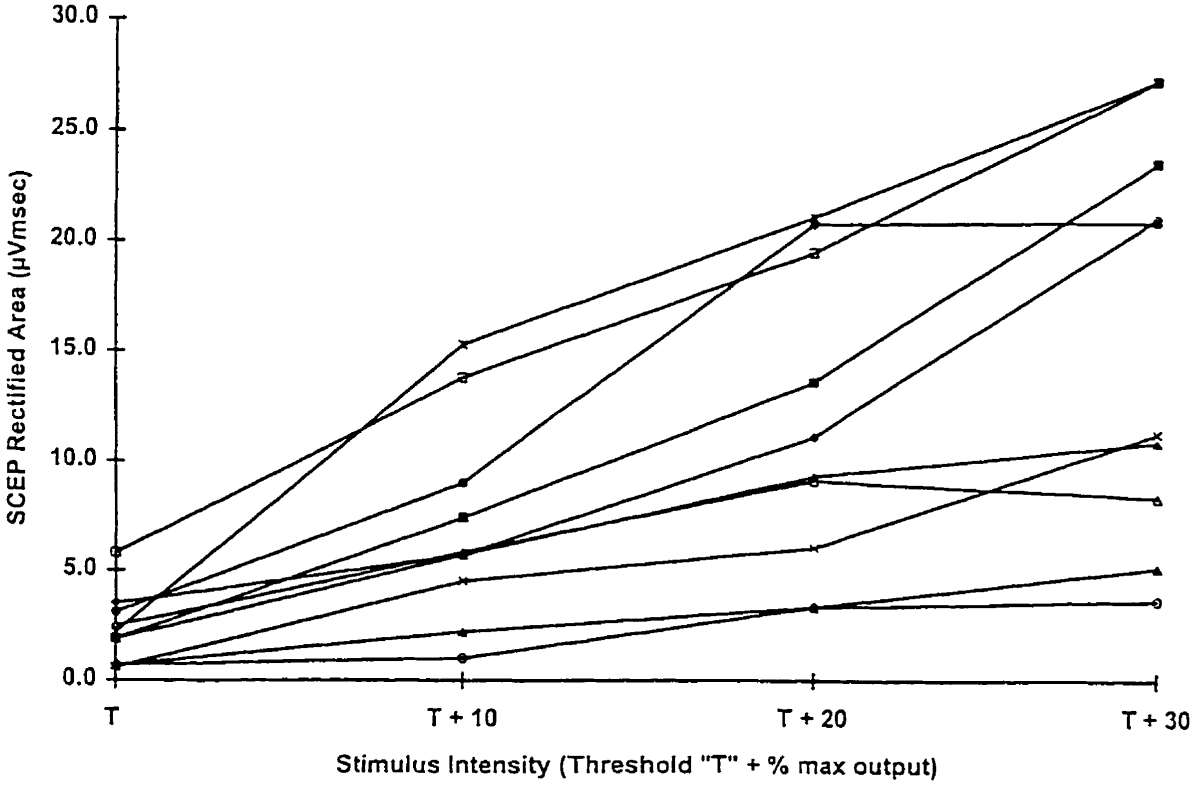
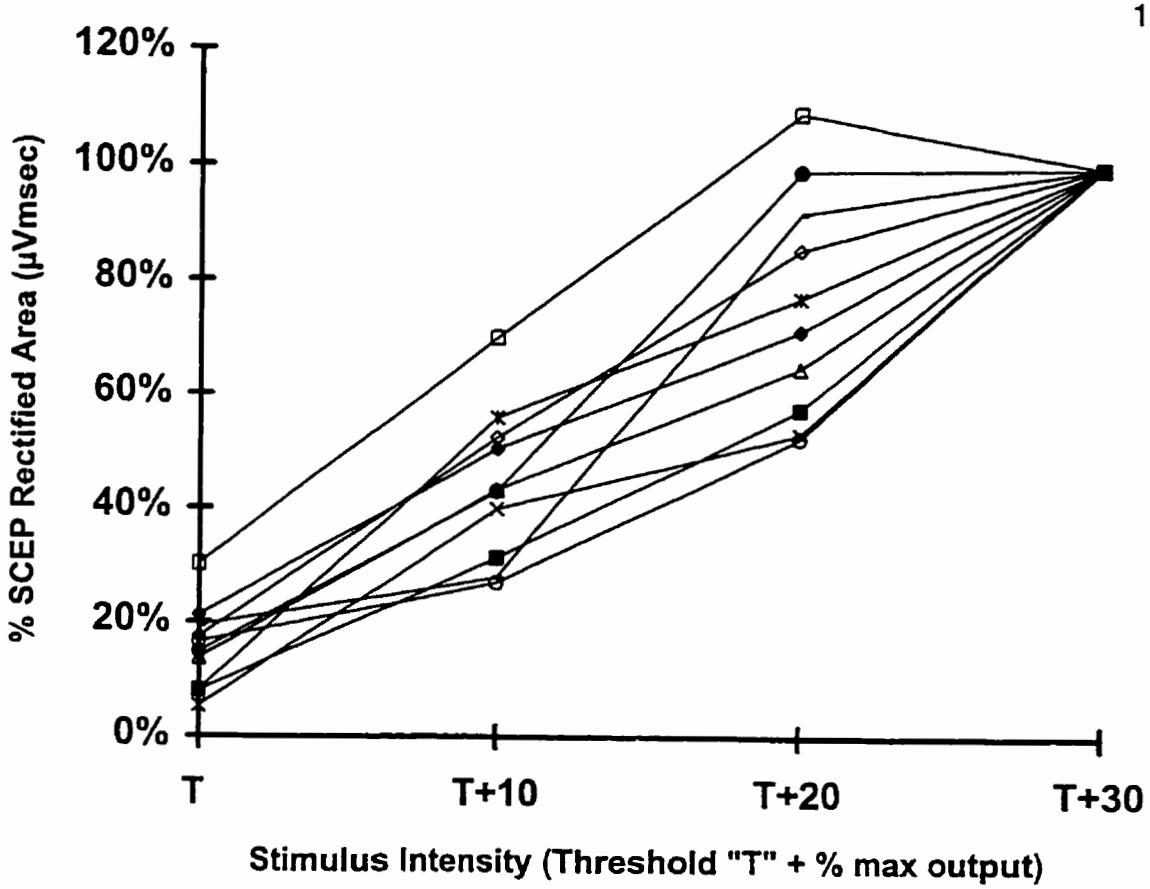


Figure 4: The effect of transcranial magnetic stimulus (TCMS) intensity on the rectified area of the SCEP recorded from an epidural electrode at Th8. The SCEP rectified area at each stimulus intensity was calculated from the average of 8 responses. **A.** The absolute SCEP rectified area at a given stimulus intensity was greatly different between subjects. **B.** The SCEP rectified area was normalized by dividing the SCEP rectified area at T + 30% by that obtained at lower stimulus intensities for each subject. The SCEP rectified area increased with increasing stimulus intensity in a similar way in all subjects.

B.


120%
100%
80%
60%
40%
20%
0%
% SCEP Rectified Area (μVmsec)
T
T+10
T+20
T+30
Stimulus Intensity (Threshold "T" + % max output)

In contrast, the latency of the D and individual I waves did not greatly change as TCMS intensity increased from T to T + 30% (figure 5). The mean amplitude, latency and interwave latency of individual D and I waves as well as the SCEP duration at T + 30% are shown in Table 1.

FDI was recruited first in most subjects despite the coil being optimally positioned for TA activation. No subjects had TA or Sol recruited at T. The effect of stimulus intensity on the order of muscle activation is shown in figure 6.

In the six subjects who had both TCMS and SBS, the rectified area, duration and maximum peak-to-peak amplitude of the SCEP after TCMS T was not significantly different than that after SBS T (Rectified Area: $T = 1.0$, $p = 0.37$; Duration: $T = 1.95$, $p = 0.11$; Maximum amplitude: $T = 0.8$, $p = 0.4$) but the pattern of muscle activation was different. FDI was recruited in 66% of subjects at TCMS T but in no subjects after SBS T. In contrast, triceps was recruited in 66% of subjects after SBS T but in no subjects after TCMS T. At higher stimulus intensities the SCEP rectified area, duration and maximum peak-to-peak amplitude after TCMS were significantly different than that after SBS.

A.

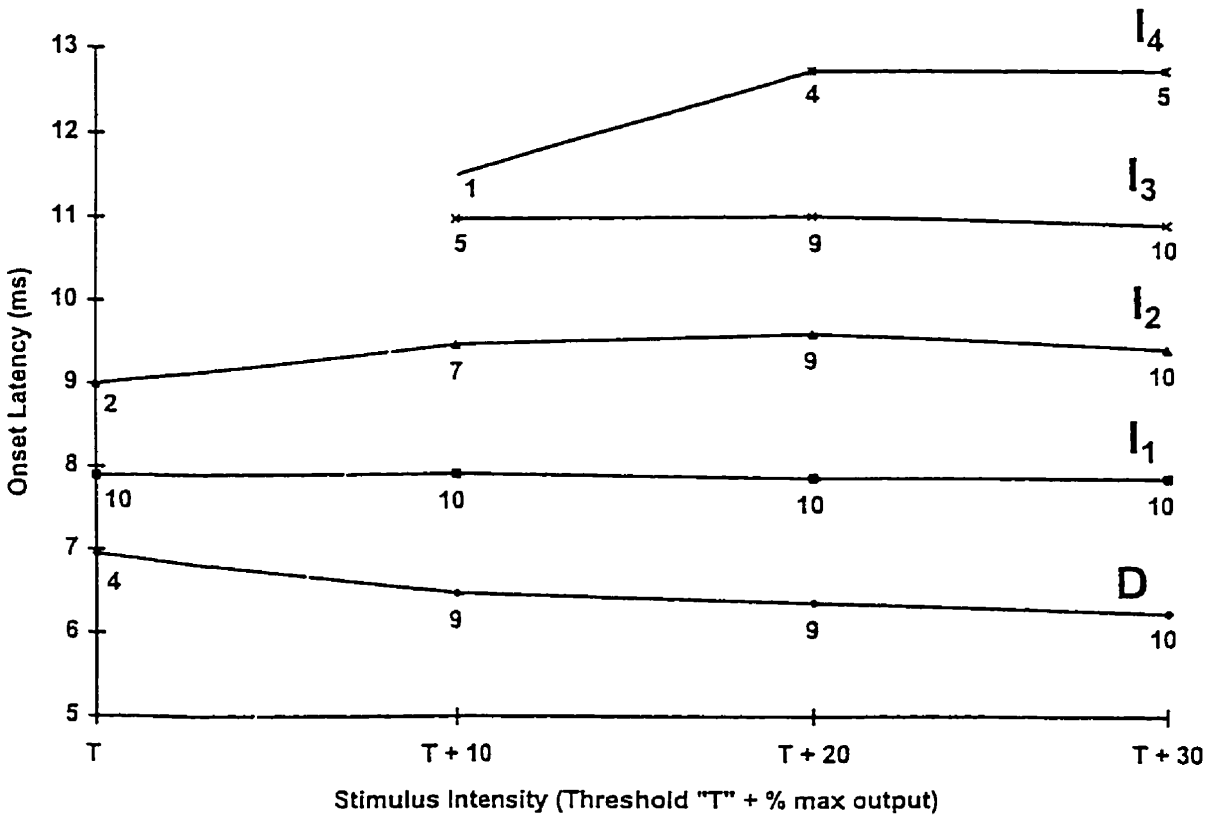


Figure 5: The effect of transcranial magnetic stimulus (TCMS) intensity on the latency of the D and I waves recorded from an epidural electrode at Th8. The number under each data point represents the number of subjects in the sample. **A.** The mean onset latency (initial negative deflection) and **B.** the mean peak latency (negative peak) of the D and I waves did not greatly change as TCMS intensity increased from T to T + 30%.

B.

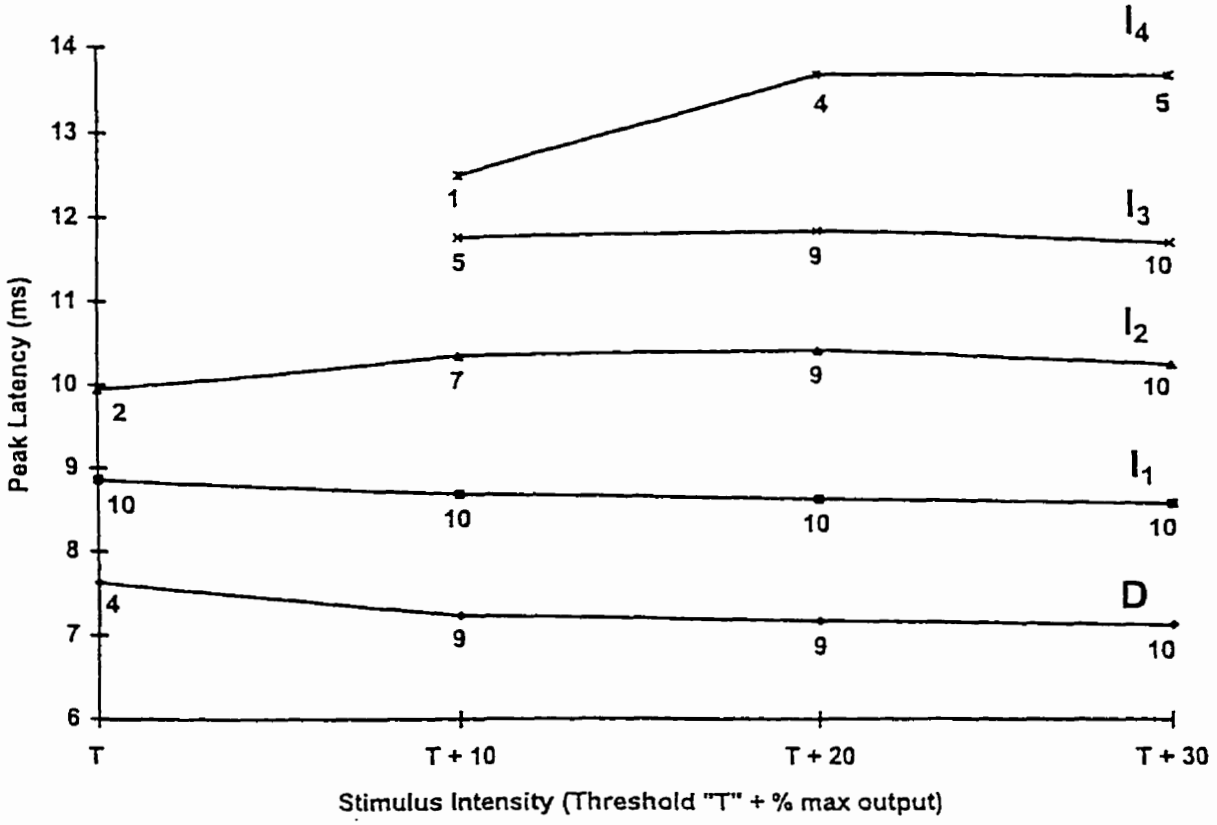

I_4
I_3
I_2
I_1
D
14
13
12
11
10
9
8
7
6
Peak Latency (ms)
1
4
5
5
9
10
2
7
9
10
10
10
10
10
4
9
9
10
T
T + 10
T + 20
T + 30
Stimulus Intensity (Threshold "T" + % max output)

TABLE 1.

NORMAL DATA FOR SPINAL CORD EVOKED POTENTIALS RECORDED AT Th8 AFTER TRANSCRANIAL MAGNETIC STIMULATION IN 10 SUBJECTS AT REST

TRANSCRANIAL MAGNETIC STIMULATION (T + 30%)

Latency (Mean ± SD)

	n = 10	n = 10	n = 10	n = 10	n = 5
wave	D	I_1	I_2	I_3	I_4
onset (ms)	6.23 ± 0.71	7.87 ± 0.67	9.45 ± 0.75	10.95 ± 0.73	12.78 ± 0.97
neg peak ms)	7.12 ± 0.59	8.59 ± 0.79	10.29 ± 0.66	11.76 ± 0.77	13.74 ± 1.02

Interwave Latency (Mean ± SD)

	n = 10	n = 10	n = 10	n = 5
waves	D - I_1	I_1 - I_2	I_2 - I_3	I_3 - I_4
onset (ms)	1.54 ± 0.13	1.58 ± 0.12	1.5 ± 0.18	1.58 ± 0.07
neg peak (ms)	1.47 ± 0.28	1.7 ± 0.18	1.43 ± 0.24	1.64 ± 0.33

SCEP Duration (Mean ± SD)

	n = 10
onset - last pos peak (ms)	7.6 ± 1.1

Amplitude (Mean ± SD)

	n = 10	n = 10	n = 10	n = 10	n = 5
wave	D	I_1	I_2	I_3	I_4
onset - neg peak (μV)	2.8 ± 2.1	4.0 ± 2.2	4.1 ± 2.9	3.6 ± 2.3	7.1 ± 3.1
neg - next pos peak (μV)	3.5 ± 2.1	5.5 ± 3.5	2.5 ± 2.3	4.0 ± 3.0	6.7 ± 4.7

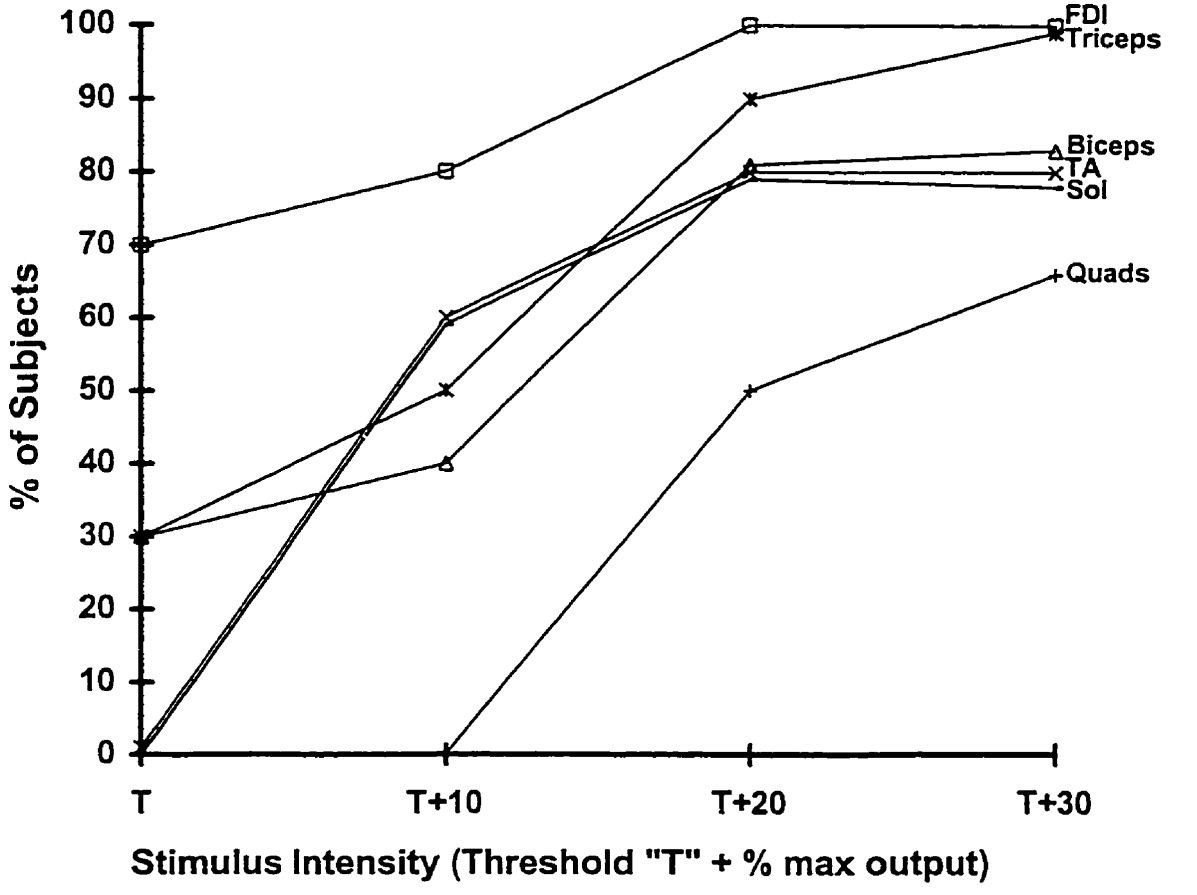


Figure 6. Order of muscle activation after TCMS (leg area) in 10 control subjects. Threshold (T) was the minimum stimulus intensity necessary to elicit a reproducible spinal cord evoked response recorded from an epidural electrode at Th8. First dorsal interosseous (FDI) was recruited at T in 70% of subjects while triceps was recruited at T in only 30% of subjects. No subjects had tibialis anterior (TA) and soleus (Sol) recruited at T.

Spinal Cord Conduction Velocity:

The latencies of the D and I waves recorded from the rostral DCS electrode (electrode one - skin surface at Th8) were shorter than those recorded from the more caudal DCS electrode (electrode three - Th8 surface) verifying that the SCEP was conducted down the long tracts of the spinal cord (Fig. 7). The change in latency of the D and I waves was similar. The conduction velocity of the D, I_1 and I_2 waves was 83 m/sec in one subject and 61 m/sec in the other which is similar to conduction velocities obtained after TCMS in anaesthetized humans (epidural recordings, range 58-65, mean 62 m/sec, Inghilleri, 1989).

Intraoperative Studies:

In the three subjects who had studies performed during inhalation anaesthesia, the D wave negative peak latency was mildly increased in all subjects (0.3, 0.8 and 0.8 ms respectively) and the D wave amplitude (onset - negative peak) was mildly reduced in all subjects (12%, 3% and 0% respectively) compared with that of the preoperative recordings obtained at the same stimulus intensity (T + 40%)(Fig. 8). The I_1 wave negative peak latency was increased in all subjects (0.6, 1.1 and 1.1 ms respectively) and the I_1 wave amplitude (onset - negative peak) was greatly diminished in all three subjects (66% and 20% and 27%

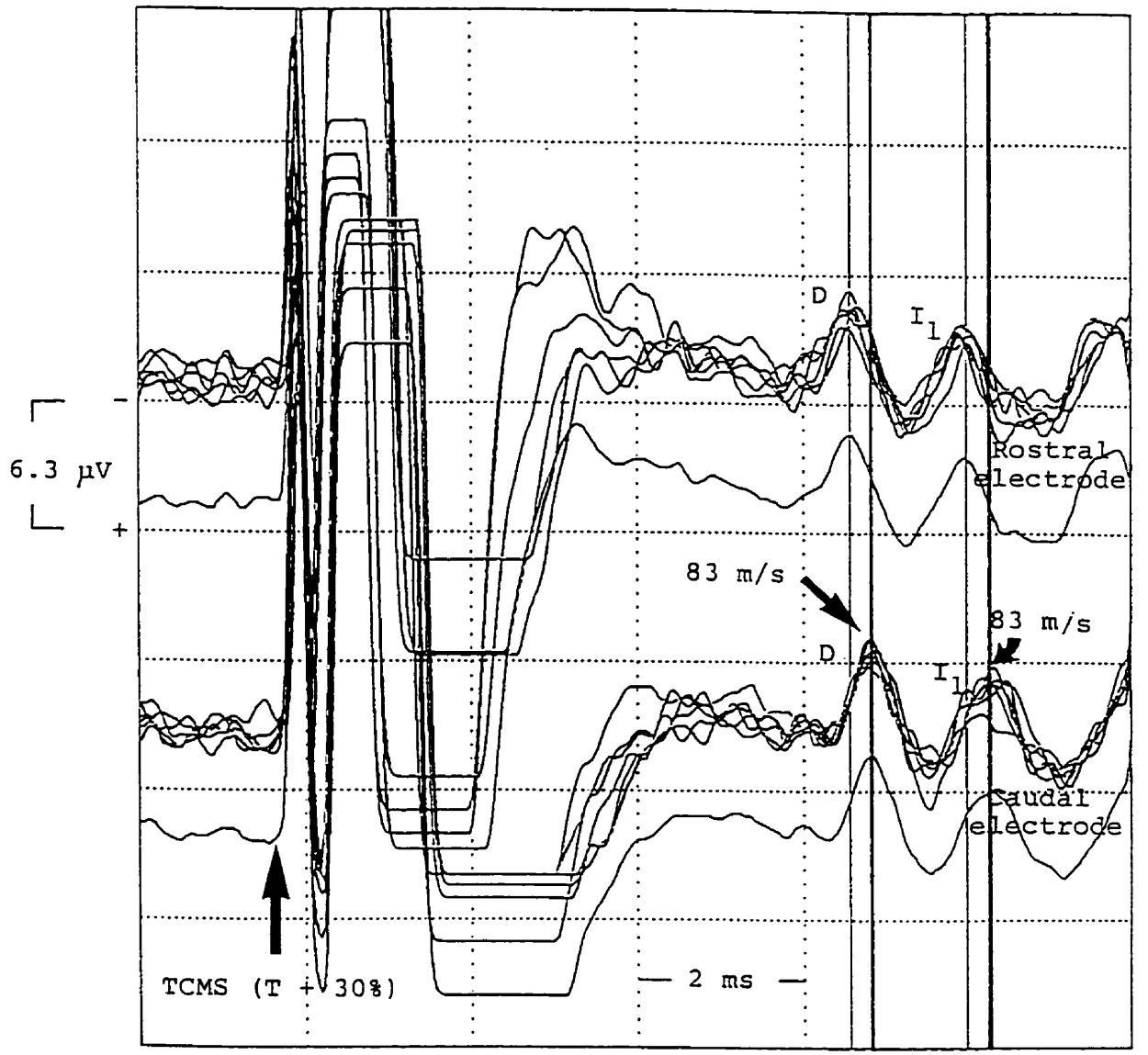


Figure 7. Descending spinal cord evoked responses (SCEPs) recorded from epidural electrodes at two different spinal cord levels (near Th8) after transcranial magnetic stimulation (TCMS) at SCEP threshold (T) + 30% in one alert subject. The epidural recording electrodes were rostro-caudally separated by 2.0 cm and each was referenced to a surface electrode (G2) over the Th8 vertebrae. The high bandpass filter was 500 Hz (bandpass 500 Hz - 5 kHz) on both channels to reduce muscle artifacts contributed by the surface electrode. The SCEP waves recorded from the rostral epidural electrode had shorter latencies than those recorded from the caudal electrode. The spinal cord conduction velocity of the D and I_1 wave was 83 meters/second.

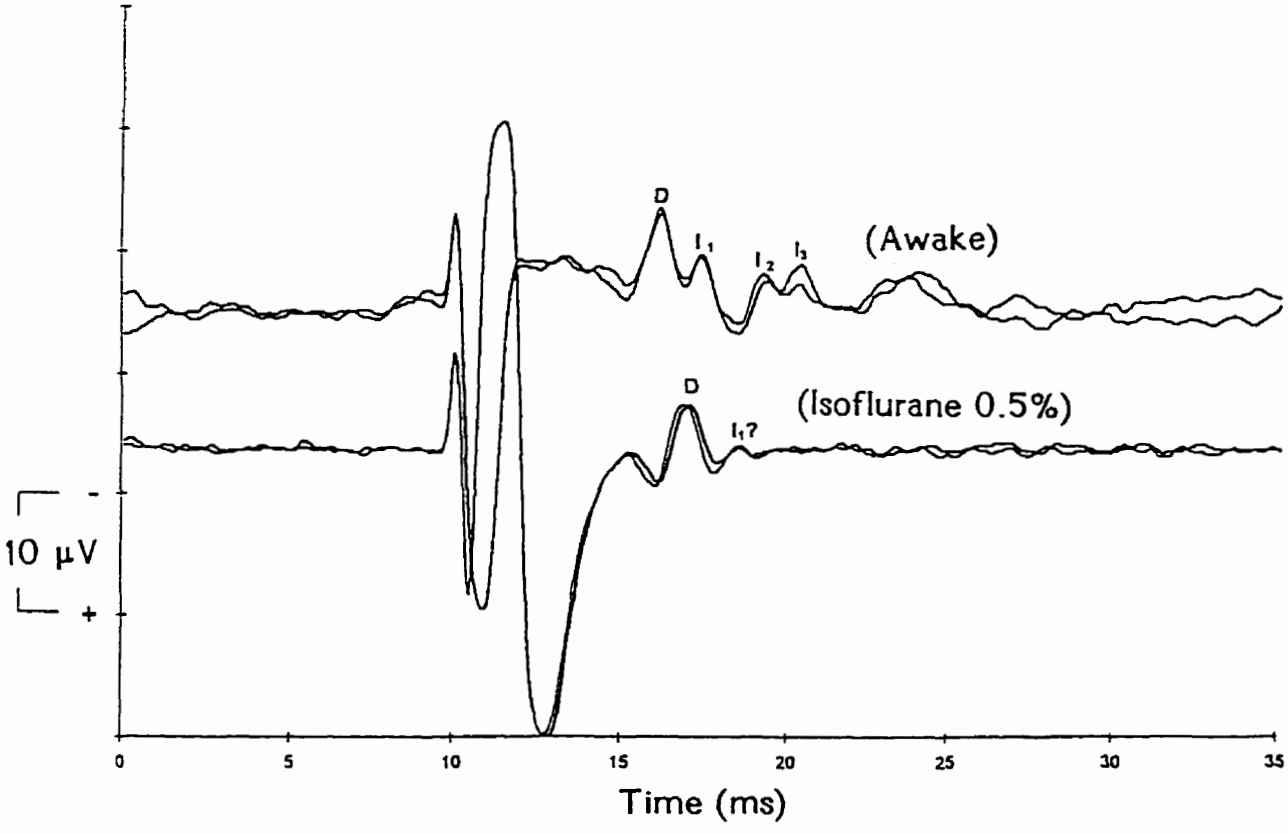


Figure 8. The effect of general anaesthetic on spinal cord evoked potentials (SCEPs) recorded from an epidural electrode at Th8 after transcranial magnetic stimulation (TCMS). The stimulus artifact occurred 9.7 ms after the onset of the sweep. When the subject was awake and at rest, the SCEP had a D wave followed by three I waves (I_1, I_2, I_3) (top trace). After the subject was anaesthetized (0.5% isoflurane, 66% N_2O, 33% O_2), the D wave was mildly prolonged and diminished, the I_1 wave was severely diminished and the I_2 and I_3 waves were absent (bottom trace) when compared to that obtained during the awake state. TCMS intensity (SCEP threshold (T) + 40% of the maximum output of the stimulator) and stimulus coil position was the same in the awake and anaesthetized conditions.

respectively) compared with that of the preoperative recordings obtained at the same stimulus intensity (T + 30%). All subsequent I waves were either absent or ill-defined. Patient temperature during intraoperative recordings was 36.1, 36.2 and 36.2◦C respectively.

Discussion

TCMS produced D and I waves which were recorded from a DCS electrode at Th8 in awake humans. The first descending wave was verified as a D wave because it had a short latency and was relatively resistant to the effects of anaesthesia when compared to the later I waves (Patton and Amassian, 1954; Katayama et al., 1988; Edgley et al., 1990; Burke et al., 1993). Although I waves were recruited at lower intensities than D waves in six of ten subjects, simultaneous recruitment of D and I waves occurred first in four subjects. D waves were recruited at marginally higher stimulus intensities (T + 10%) in all subjects. These findings from awake humans are in accordance with those obtained from non-human primates anaesthetized by pentobarbital (Amassian et al., 1990) but disagree with results from humans anaesthetized by N_2O and fentanyl where D wave threshold after TCMS was found to be the same as or slightly lower than I wave threshold (Burke et al., 1993) This discrepancy may be related to the depressive effects of anaesthesia on SCEPs. Perhaps nitrous

oxide had a greater depressive effect than pentobarbital on the indirect excitation of corticospinal neurons after TCMS in these studies.

The minimum TCMS intensity sufficient for activation of one or two SCEP waves (T) (40 - 60% of the maximum output of the stimulator) was insufficient for activation of leg muscles in our relaxed subjects. Leg muscle responses were not recruited at SCEP T during rest probably because only one or two low amplitude SCEP waves were activated which was insufficient for the spatial and temporal summation necessary for depolarization of spinal motoneurons. Higher TCMS intensities recruited at least four SCEP waves which was sufficient for activation of leg muscles.

The D and I waves we recorded at Th8 represented cortical outflow from corticospinal neurons supplying the trunk and lower extremity. The pyramidal cells for the lower extremities are located in the anterior bank of the central sulcus (paracentral lobule) so some may lie parallel to the induced current when the coil is tangentially oriented on the top of the head (Amassian et al., 1989) since pyramidal cells and their apical dendrites are orientated perpendicular to the cortical surface. The amount of cellular polarization is increased when the stimulus current flow is parallel to the cell's neural axis (Rushton, 1927; Toleikis et al., 1974; Roth and Basser, 1990) so a coil oriented tangential to the top of head may directly excite corticospinal neurons for the lower extremity or their

axons at the first bend (Amassian et al., 1992). The coil position we used (mean = 4 cm anterior and 1.6 cm to the left of vertex) was suitable for optimal activation of corticospinal neurons in the leg area of the motor cortex (near vertex) because, for our coil, the largest induced current occurs 4.3 cm from the centre of the coil in a plane parallel to the coil (Meyer et al., 1991). I waves also occurred at low stimulus intensities suggesting the cortico-cortical axons activated after TCMS were orientated parallel to the current flow probably running posteriorly from premotor cortex, or anteriorly from postcentral gyrus to precentral gyrus (Day et al., 1986; Day et al., 1989; Amassian et al., 1989; Amassian et al., 1990). Alternately, it is possible that the descending pathways from the postcentral gyrus contributed to the SCEP because the primary sensory cortex is located beside the primary motor cortex and contains corticospinal neurons that project to the dorsal horn (Willis and Grossman, 1981; Brodal, 1981). This was unlikely because motor cortex ablation in monkeys obliterated all D and I waves after stimulation of the primary sensory cortex (Patton and Amassian, 1960). Furthermore, dorsal column transection did not affect the SCEP originating from the sensorimotor cortex after TCMS in cats (Kawai and Nagao, 1992).

Other descending pathways may have been directly or indirectly activated by TCMS and contributed to the SCEP and muscle responses. The lateral vestibulospinal pathway is fast conducting with mono- and polysynaptic

connections in the spinal cord that are predominantly ipsilateral (Nyberg-Hansen and Mascitti, 1964) but the muscle responses after TCMS are primarily contralateral to side of stimulation (Toleikis et al., 1991; Tarao et al., 1994). The reticulospinal pathway is also fast conducting with mono- and polysynaptic connections in the spinal cord that activate primarily proximal muscles bilaterally (Peterson et al., 1979) but this is in contrast to the pattern of activation after TCMS (Brouwer and Ashby, 1990; Rothwell et al., 1987). Our knowledge of other descending motor pathways (rubrospinal, interstitiospinal, tectospinal) in man is limited (Rothwell et al., 1987). Accordingly, the pathways mediating the earliest effects of cortical stimulation have been termed, "corticomotoneuronal" (Bernhard and Bohm, 1954; Rothwell et al., 1987).

TA responses appeared to be dependent on the SCEP waves. For example, the presence of the SCEP was associated with muscle responses and larger, more complex SCEPs were associated with larger muscle responses (Figs. 1 and 7). This was demonstrated in the two subjects without TA responses at T + 30% but when TCMS increased, another I wave or larger I waves was associated with a TA responses. Furthermore, the interwave latencies of D and I waves we recorded from surface spinal cord electrodes in awake humans closely resemble and have similar conduction velocities to those recorded from single fibres in the lateral corticospinal tract and from the surface of the spinal cord following direct electrical stimulation of the motor cortex in baboons

(Kernell and Wu, 1967). In subhuman primates, a single electrical stimulus to the motor cortex produced I waves that were recorded from single fibres in the lateral corticospinal tract (Kernell and Wu, 1967). The I waves they recorded originated from synchronous repetitive discharges in the same group of pyramidal cells that created the D wave. Consequently, the D and I waves recorded from single fibres had similar amplitudes. In surface recordings, the compound D wave they recorded was larger than the compound I waves probably due to variability of I wave response latencies resulting in phase cancellation when recorded from the surface of the spinal cord (Patton and Amassian, 1954; Amassian et al., 1987b). In contrast, we and others have found the amplitude of the I waves after TCMS (coil oriented tangential to skull at vertex) was often greater than that of the D wave when recorded from the surface of the spinal cord in humans (Edgley et al., 1991; Burke et al., 1993). This suggests that many of the corticospinal neurons contributing to the I waves may not have contributed to the D wave after TCMS (Edgley et al., 1991; Burke et al., 1993). This discrepancy is not due to the difference between single fibre and surface recordings because surface recordings underestimate I responses (Patton and Amassian 1954; Amassian et al., 1987b). Instead, this finding may be related to the difference in stimulating techniques because direct electrical stimulation of the motor cortex may excite corticospinal neurons differently (ie. more discretely, more directly) than TCMS thereby creating larger D waves. Conversely, TCMS (coil oriented tangential to skull at vertex) may indirectly

activate corticospinal neurons better than direct electrical stimulation by exciting more cortico-cortical inputs to corticospinal neurons and/or creating more synchronous indirect activation of corticospinal neurons. Nevertheless, we found the interwave latencies between D and I waves did not change greatly as TCMS intensity increased suggesting the synchronous repetitive discharges of corticospinal neurons had a rigorous temporal code. Furthermore, the onset latencies to the D and I waves did not greatly change as TCMS intensity increased suggesting descending pathways located more caudally in the brain were not excited at higher stimulus intensities. The D and I wave conduction velocity of 83 and 61 m/sec is similar to the 62 m/s previously recorded from epidural spinal cord electrodes after TCMS in anaesthetized humans (Inghilleri et al., 1989).

A minimum of four SCEP waves (D, I_1, I_2, I_3) were necessary for activation of the TA in all ten subjects at rest. This supports previous work which has shown that depolarization of alpha motoneurons results from the summation effects of later I waves (Day et al., 1987; Mills, 1991) Previous investigators have estimated the effect of D and I waves on the TA motoneuron pool in man after low intensity TCMS using peri-stimulus-time histograms (PSTHs) (Awiszus and Feistner, 1994). They recorded two PSTH subpeaks after TCMS which were thought to represent the effect of the D wave (first positive peak) followed 3 - 4 ms later by the effect of the I_3 wave (second positive peak). These conclusions

are based on the assumption that the form of the PSTH reflects the differential of the time course of the compound EPSP at the spinal motoneuron created by the arrival of individual D and I waves (Day et al., 1989). Our results confirm the importance of I waves (especially I_3) for activation of TA, but our D - I_3 interwave latency following low intensity TCMS (mean = 4.6 ± 0.3 ms) was longer than the 3 - 4 ms previously estimated by the PSTHs (Awizsus and Feistner, 1994). Perhaps the PSTH positive peak previously attributed to the D wave was really related to I_1 because our I_1 - I_3 interwave latency was between 3 - 4 ms (mean = 3.2 ± 0.2) and I_1 was recruited first at low TCMS intensities in six of our ten subjects.

Comparison of SCEP after SBS to that after TCMS:

The SCEP after SBS contained a single volley while that after TCMS contained up to six volleys. The waves after TCMS were similar to the D and I waves previously recorded from the spinal cord of anaesthetized monkeys after surface anodal stimulation of the brain (Patton and Amassian, 1954).

TCMS indirectly and directly activated corticospinal neurons in the brain and the resultant D and I waves were temporally coded to allow for efficient motoneuron depolarization in the lumbo-sacral spinal cord by temporal summation. In

contrast, SBS activated long tracts in the caudal brainstem or high spinal cord resulting in a single wave of depolarization that could not use temporal summation as a tool for motoneuron depolarization. At stimulus intensities above T, the peak-to-peak amplitude of the SCEP after SBS was significantly larger than that after TCMS, as previously predicted (Ugawa et al., 1991b; Berardelli et al., 1991), but it was less effective at depolarizing TA and Sol alpha motoneurons because it did not contain multiple descending waves.

The different pattern of muscle activation after TCMS and SBS at low stimulus intensities (T) was not a function of different SCEP characteristics. The SCEP after SBS was not significantly different in rectified area, duration or peak-to-peak amplitude than that after TCMS at T, yet the SBS activated alpha motoneurons differently than TCMS at T. SBS produced strong excitation to triceps motoneurons while TCMS excited FDI motoneurons at T as previously demonstrated (Brouwer and Ashby, 1990; Alstermark and Sasaki, 1985).

At higher stimulus intensities (TCMS T + 10% to T + 30% and SBS T + 7.5% to T + 22.5%), the SCEP after SBS was significantly different than that after TCMS. The SCEP duration after TCMS became significantly longer than that after SBS because more waves were recruited as stimulus intensity increased. Nevertheless, the different pattern of activation after SBS and TCMS at these stimulus intensities cannot be explained by temporal summation alone unless it

is argued that the motoneurons preferentially activated by TCMS are dependent on temporal summation and the others are not. Instead, the difference in order of activation between TCMS and SBS may be due to the location of stimulation as it relates to the excitability of neurons in the brain and spinal cord. For example, muscle activation after TCMS is dependent on the excitability of corticospinal neurons in the brain as well as the excitability of spinal motoneurons while muscle activation after SBS is dependent only on spinal motoneuron excitability and the long tracts activated by SBS. It is likely that TCMS inhibited some corticospinal neurons and excited others by activation of inhibitory and excitatory cortico-cortical connections. A single stimulus to the brain has been shown to reduce the excitability of cortical neurones for up to 300 ms related to GABAergic activity involving basket cells and probably other cells in the grey matter (Krnjevic et al., 1966; Krnjevic et al., 1983) creating a true IPSP and not disfacilitation (Rosenthal et al., 1967). The degree to which cortical inhibition plays a role in the order of activation of corticospinal neurons and subsequent muscle recruitment pattern is unknown. The IPSPs in the motor cortex are generated after the D and I waves and have a longer latency than the EPSPs (Rosenthal et al., 1967).

SBS activated descending pathways sub-cortically so cortico-cortical connections could not affect the distribution of drive on spinal motoneurons. Furthermore, SBS was not discrete and probably activated a wide variety of

motor tracts at the skull base (ie. corticospinal pathways, lateral and medial brainstem-spinal pathways, bulbospinal pathways, dorsal columns, propriospinal pathways).

The SCEP after TCMS was more affected by anaesthesia than the SCEP after SBS because the I waves after TCMS were dependent on synaptic activity that is depressed during inhalation anaesthesia. The D wave was less affected because it likely reflected direct activation of the corticospinal axon (at the first bend) and/or the corticospinal cell itself which was less dependent on synaptic transmission than the cortico-cortical connections that are necessary for I wave generation (Edgley et al., 1990; Amassian et al., 1990; Amassian et al., 1992). In contrast, the single wave after SBS was not dependent on synaptic activity which verified it was the result of activation of long tracts in the high spinal cord/low medulla. The increase in SCEP latency may have been due to a change in DCS recording electrode position to a more caudal location on the spinal cord after the patient was placed prone on the operating table and/or decreased patient temperature. It is also possible that anaesthesia changed cerebral blood flow and the electrical field induced in the volume conductor resulting in a more distal site of corticospinal neuron activation at another bend in the corticospinal neuron trajectory (Amassian et al., 1992).

The D and I_1 waves after TCMS had similar conduction velocities suggesting

both were conducted in the same pathway. The conduction velocity of the D and I_1 waves at the Th8 spinal cord was fast at 83 m/sec in one subject and 61 m/sec in another. These SCEP conduction velocities after TCMS were slower than those estimated after SBS (mean = 94 m/sec after SBS, see Chapter 5) but that does not necessarily mean they were conducted in different pathways as there are inherent errors associated with the measurement of conduction velocity (see Chapter 5) and there is considerable overlap in the range of conduction velocity for fast conducting pathways like the corticospinal, rubrospinal, vestibulospinal, reticulospinal and dorsal spinocerebellar pathways (Woolsey and Chang, 1948; Levy, 1983; Levy et al., 1986; Bantli et al., 1975; Bloedel and Bantli, 1978; Brodal, 1981; Eccles et al., 1974; Patton and Amassian, 1954; Lund and Pompeiano, 1965).

Implications For Intraoperative Spinal Cord Monitoring:

Non-invasive intraoperative monitoring using bilateral muscle responses after TCMS is desirable, but difficult, because inhalation anaesthesia greatly decreases the amplitude of muscle responses after TCMS. The decrease in muscle response amplitude is thought to be due to the depressive effect that anaesthesia has on the trans-synaptically generated I waves. Recent intraoperative studies have shown that a short train of repetitive electrical brain

stimulation, using stimuli with short inter-stimulus intervals, may replace I waves (obliterated by anaesthesia) with a train of D waves resulting in activation of muscles that were previously silent after a single stimulus (Taniguchi et al., 1993; Kalkman, 1994; Jones et al., 1996). In awake subjects, we found that four SCEP waves (D, I_1, I_2, I_3) were necessary for leg muscle activation and the interwave latencies had a rigorous temporal code so, in anaesthetized patients, the optimal stimulation parameters for activation of leg muscles may be those that artificially recreate the four SCEP waves seen in awake subjects.

In summary, the neurophysiological outflow after TCMS and SBS was recorded directly from the spinal cord in awake human subjects for the first time. The descending volleys after TCMS and SBS had fast conduction velocities but they contained a different number of waves and had different durations and amplitudes. TCMS evoked a descending volley consisting of a D wave followed by three or four I waves that were reliably recorded by the DCS electrode in all subjects. Presence of the D and I waves in all subjects at low stimulus intensities verified that TCMS directly and indirectly activated corticospinal neurons in the sensorimotor cortex. Leg muscle responses after TCMS in awake subjects were usually contingent on a descending SCEP containing at least four waves. The SCEP after SBS contained a single wave and was less effective than TCMS in activating leg muscles.

The TCMS threshold for activation of leg muscles is lower when the target muscle is voluntarily activated. It has been postulated that voluntary activation of leg muscles during TCMS increases the excitability of spinal motoneurons such that EPSPs from only one or two low amplitude SCEP waves are necessary for alpha motoneuron depolarization (Day et al, 1987). Alternately, it has been postulated that cortical excitability increases during voluntary activation of leg muscles which increases the amplitude and/or number of waves in the descending SCEP resulting in better spatial and temporal summation of descending activity on spinal motoneurons (Baker et al., 1995). The next chapter will demonstrate that increases in both cortical excitability and spinal motoneuron excitability may occur during voluntary activation of TA but the increases in cortical excitability are only detectable at low TCMS intensities.

CHAPTER VII

Effects Of Voluntary Activation On SCEPs And Muscle Responses After TCMS In Awake Human Subjects

Abstract

Facilitation of muscle responses after transcranial magnetic stimulation (TCMS) during a voluntary muscle contraction is thought to be due to increased motor cortical excitability and/or increased excitability at the spinal motoneuron pool but the precise mechanism is not known. To elucidate the mechanism responsible for facilitation, we recorded spinal cord evoked potential (SCEPs) and muscle responses after TCMS during rest and voluntary contraction of left tibialis anterior (TA) in seven awake, neurologically intact subjects.

Corticospinal neuron excitability was determined by the amplitude, latency and rectified area of SCEPs recorded from an epidural dorsal column stimulating electrode at Th8 after TCMS. Muscle recordings were concomitantly recorded from the left biceps, triceps, first dorsal interosseous, tibialis anterior (TA) and soleus. The magnetic stimulator coil was positioned for optimal activation of the left TA. SCEP and muscle responses were obtained as TCMS intensity increased from threshold ("T") for activation of a SCEP, to T + 30% of the maximum output of the stimulator in 3 equal steps. At each stimulus intensity, recordings were obtained at rest and during voluntary contraction of TA in an alternating fashion. The SCEP rectified area was not significantly increased during voluntary activation of TA, compared to rest, across all TCMS intensities (Raw data: $F=1.6$, $p=0.25$; Log data: $F=2.67$, $p=0.15$) except at T (Raw data: $T=2.3$, $p=0.03$; Log data: $T=2.97$, $p=0.01$). Voluntary contraction of TA

significantly increased the amplitude of the TA muscle response, compared to rest, across all TCMS stimulus intensities (Raw data: $F=6.6$, $p=0.04$; Log data: $F=23.6$, $p=0.003$).

Increased excitability of corticospinal neurons during voluntary activation of TA (indicated by increased SCEP rectified area) was observed at T but not at TCMS intensities above T. It is proposed that TCMS intensities above T, during rest, activated a) a greater percentage of corticospinal neurons not subserving TA whose excitability did not increase and/or b) a greater percentage of the total cortical area available for increased excitability, thereby overshadowing the small, discrete increase in corticospinal neuron excitability that was observed at T during voluntary activation of TA.

Introduction

A minimal amount of voluntary muscle contraction increases the amplitude of evoked muscle responses after transcranial electric stimulation (TCES) or transcranial magnetic stimulation (TCMS) (Hess, 1986; Barker et al., 1987; Caramia et al., 1989; Rothwell et al., 1991; Pereon et al., 1995). This muscle facilitation may be due to increased motor cortical excitability (Baker et al., 1995) or increased excitability at the spinal motoneuron pool (Day et al., 1987) or both. There is no direct evidence in humans to support increased motor cortical excitability during voluntary contraction because it is difficult to directly measure the output from the motor cortex before it reaches the spinal motoneuron pool in awake intact humans. Evoked responses recorded directly from the medulla after TCMS in the monkey (Baker et al., 1995) have shown a task-related increase in the amplitude of the initial descending volley (output from the motor cortex) implying increased cortical excitability during performance of a motor task. In contrast, H reflex studies in humans have shown that the threshold of the initial descending volley (measured by PSTHs) produced by TCES is unaffected by a voluntary contraction (Day et al., 1987).

The previous chapter described D and I waves recorded directly from the spinal cord after TCMS in ten awake subjects with dorsal column stimulators (DCS). This indicated that TCMS directly and indirectly activates corticospinal neurons. The rectified area of the SCEP and the muscle response amplitude increased with TCMS

intensity indicating more corticospinal neurons were excited with increasing stimulus intensity in these resting subjects.

This chapter compared SCEP and muscle responses during rest and voluntary activation of TA in seven of those ten subjects. It was hypothesized that the excitability of corticospinal neurons would increase during voluntary activation of left TA so that TCMS would activate more corticospinal neurons and increase the rectified area of the SCEP.

Methods

Subjects:

Experiments were performed on seven subjects (6 male) aged 35 - 59 years (mean 49 years) who underwent surgery for DCS implantation to control pain resulting from failed back syndrome (four subjects) arachnoiditis following lower back surgery (two subjects) and prostatitis (one subject). These subjects also participated in the experiment described in the previous chapter. Analgesic medication was stopped several hours prior to the experiment and no analgesics were given during the experiments. All patients had normal motor and sensory examinations. All experimental methods described below were approved by the Research Ethics Board

at Sunnybrook Health Science Centre and all patients gave their informed consent to participate in the experiments.

Stimulating and Recording Techniques:

The SCEP and muscle responses after TCMS were obtained in the manner described in Chapter 2. Recordings were obtained at rest and during voluntary activation of the left TA at TCMS intensity T, T + 10, T + 20% and T + 30%. Voluntary activation of TA was maintained at 10% maximum voluntary contraction as measured by an EMG biofeedback machine (Model 4081, Hyperion Inc., Miami, FL). The electrodes used for biofeedback were positioned 3 cm apart beside the TA recording electrodes already in position for recording muscle responses after TCMS. The biofeedback machine provided auditory and visual feedback of rectified EMG to the subject. TCMS was delivered as soon as 10% maximum voluntary TA contraction was achieved. To ensure only TA was activated, relaxation of the other muscles was monitored by a live EMG display and an EMG audio monitor of each channel on the Cadwell Excel evoked potential machine. At each stimulus intensity, trials in which TA was activated were alternated with trials where the subjects were relaxed.

Data Analysis:

The SCEP was the average of three to five responses. A minimum of two SCEP averages were superimposed for waveform reproducibility for each condition (relaxed and TA activated). The average of two muscle responses were obtained for each muscle. Typically, the muscle recordings were obtained at the beginning of each SCEP average. The SCEPs and muscle responses were measured in the manner described in Chapter 2. The overall effect of voluntary activation of TA on SCEP rectified area and TA response amplitude across all stimulus intensities was measured by ANOVA. The SCEP rectified area obtained during rest was compared to that obtained during voluntary activation of TA at each stimulus intensity using paired *t* tests. The statistical procedures (ANOVA, *t* test) were repeated using the natural logarithm of SCEP rectified area and TA response amplitude.

Results

The mean centre coil position for optimal activation of left TA was 3.8 ± 0.6 cm anterior and 3.6 ± 0.8 cm to the left of Cz for the seven subjects who participated in the experiment. The SCEP T varied between 40 - 60% of the maximum output of the stimulator (mean = 50 ± 8). At this stimulus intensity the SCEP contained D and I_1 waves in three subjects, an I_1 wave alone in three subjects, and I_1 and I_2 waves in one

subject.

The two-way ANOVA results showed a significant effect of condition (rest, TA activated) on TA amplitude indicating that TA response amplitude significantly increased during voluntary activation of TA, compared to rest, across all TCMS intensities (Raw data: $F=6.6$, $p=0.04$; Log data: $F=23.8$, $p=0.003$). There was also a significant effect of TCMS intensity on the muscle response amplitude (Raw data: $F=7.9$, $p=0.02$; Log data: $F=19.2$, $p=0.002$) and a significant interaction between condition and TCMS intensity when analyzing the raw data (Raw data: $F=5.7$, $p=0.037$).

The two-way ANOVA results showed a highly significant effect of TCMS intensity on SCEP rectified area (Raw data: $F=12.4$, $p=0.005$; Log data: $F=88.8$, $p=0.0001$). In contrast, there was no significant effect of condition (rest, TA activated) on the SCEP rectified area indicating that SCEP rectified area did not significantly change during voluntary activation of TA, compared to rest, across all stimulus intensities (Raw data: $F=1.6$, $p=0.25$; Log data: $F=2.67$, $p=0.15$). Similarly, there was no significant interaction between condition and TCMS intensity (Raw data: $F=1.2$, $p=0.32$; Log data: $F=1.3$, $p=0.31$). The effect of voluntary activation of TA on the SCEP and muscle responses for one subject is shown in figure 1.

The effects of condition on SCEP rectified area were evaluated separately at each

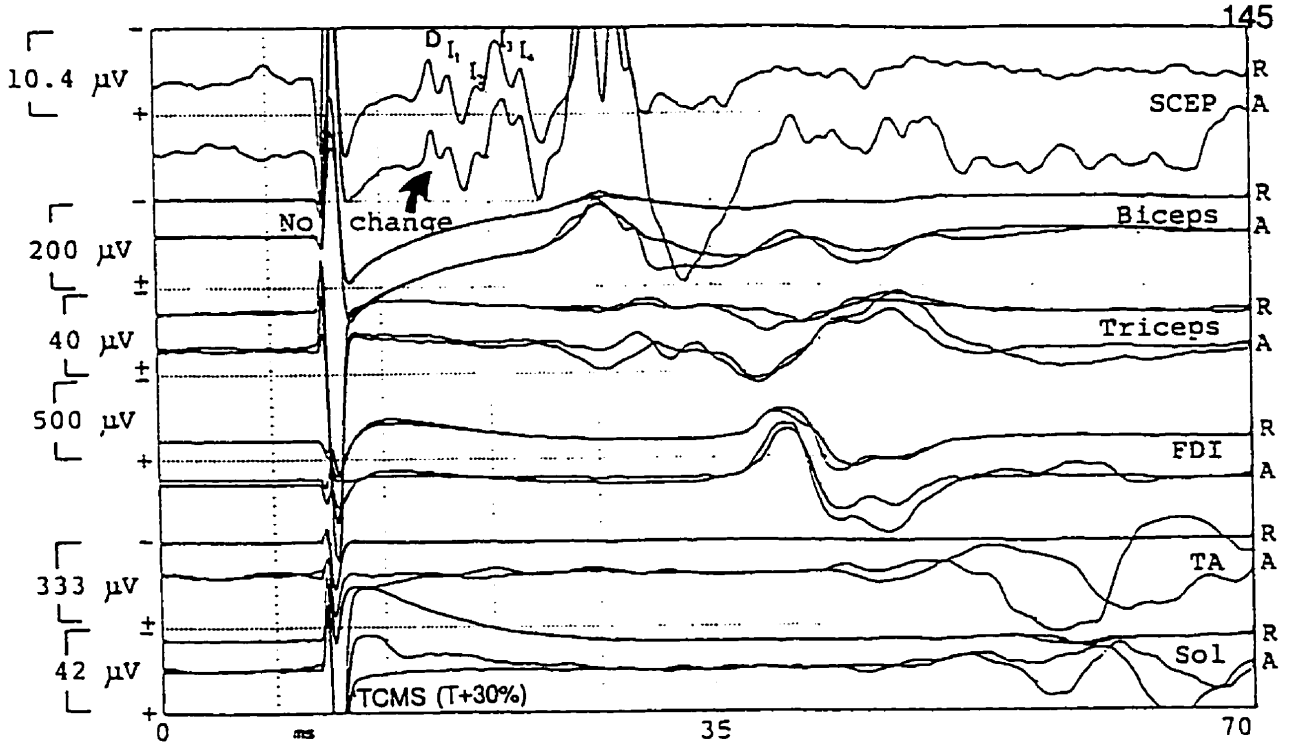


Figure 1. The effect of voluntary activation (10% of maximum voluntary contraction) of tibialis anterior (TA) on the spinal cord evoked response (SCEP) and muscle responses after transcranial magnetic stimulation (TCMS) using a high stimulus intensity (SCEP threshold (T) + 30% maximum output of the stimulator) in one subject. The SCEP was recorded from an epidural electrode at Th8. The traces obtained at rest are designated "R" and the traces obtained during activation of the TA are designated "A" as displayed on the right hand side of the figure. During voluntary activation of TA there was facilitation of the biceps, triceps, first dorsal interosseous (FDI), TA and soleus (Sol) muscle responses but no change in the SCEP D and I waves compared with that obtained at rest when the same TCMS intensity was used. The response occurring after I_4, that was facilitated during activation of TA, was probably myogenically generated. Each SCEP is the grand average of 8 responses. Each muscle response trace consists of 2 single superimposed responses.

TCMS intensity by paired *t* tests because the overwhelming effect of TCMS intensity on SCEP rectified area may have obscured the smaller effects of condition. At TCMS T, there was a significant increase in SCEP rectified area during voluntary activation of TA, compared to rest when analyzed by paired *t* test (Raw data: T=2.3, df=6, p=0.03; Log data: T=2.97, df=6, p=0.01 and with Bonferroni correction, p=0.05). The mean latency of the initial negative deflection of the SCEP at T did not significantly change when comparing rest and TA preactivated conditions at T (T=1.32, p=0.117). The effect of voluntary activation of TA on SCEP amplitude and rectified area after low intensity TCMS (T) for one subject is shown in figure 2. At higher TCMS intensities there was no significant increase in SCEP rectified area during voluntary activation of TA, compared to rest when analyzed by paired *t* test (Raw data: (at T+10%) T=0.5, p=0.31; (at T+20%) T=1.1, p=0.15; (at T+30%) T=1.41, p=0.1; Log data: (at T+10%) T=0.4, p=0.35; (at T+20%) T=0.4, p=0.34; (at T+30%) T=1.42, p=0.1)

The mean percent change in SCEP rectified area during voluntary activation of TA across all stimulus intensities is shown in figure 3. The variability of the percent change in SCEP area increased as stimulus intensity increased from T to T + 10%. At TCMS T, the SCEP rectified area increased in all subjects (mean ± SD = 12.3% ± 10%; range = 1 - 29%) but at TCMS T + 10% the SCEP area increased in some subjects and decreased in others (mean ± SD = 4.8% ± 22.5%; range = -13 - 54%).

During rest, the TA response at T was absent in all seven subjects and the SCEP

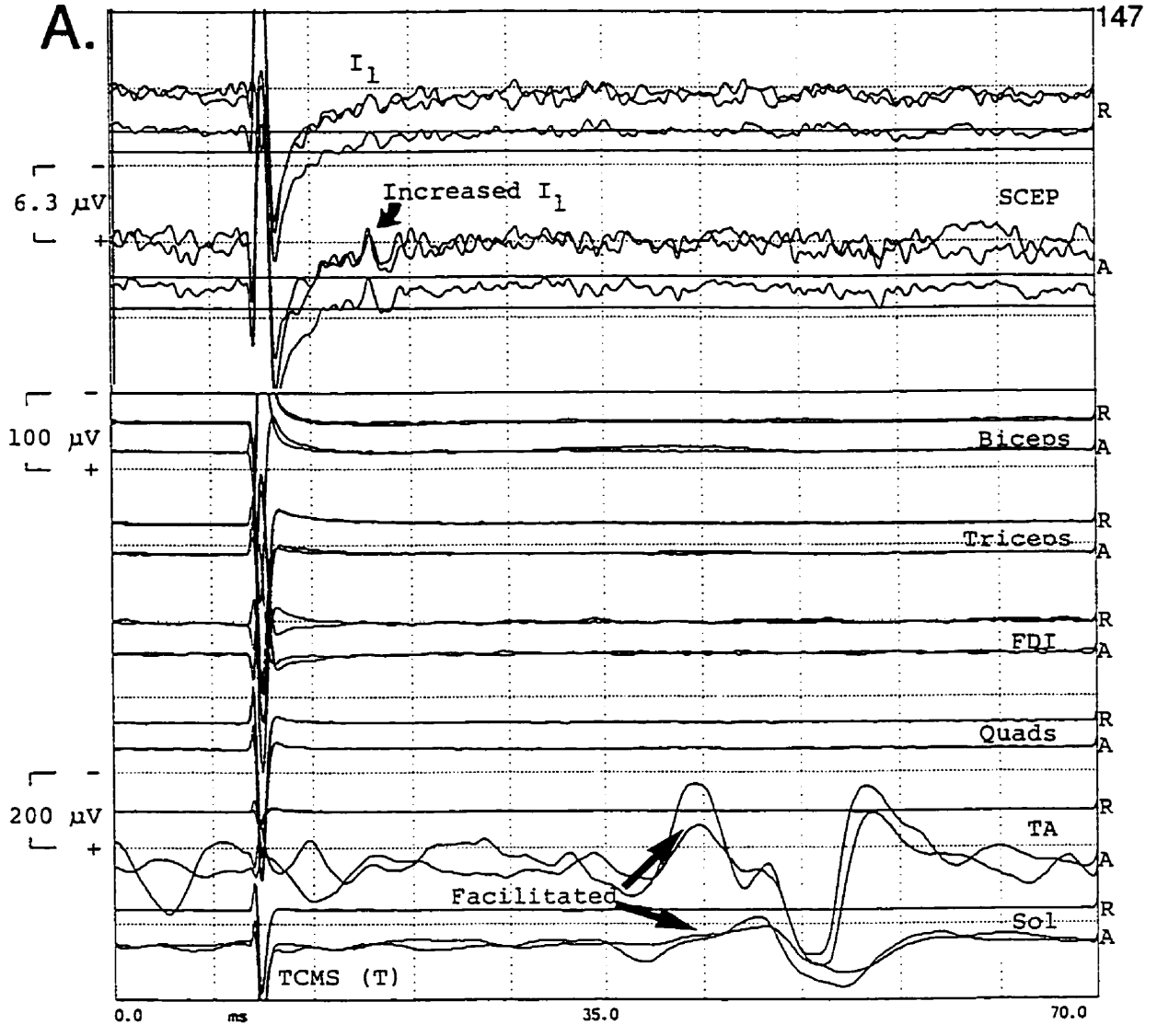
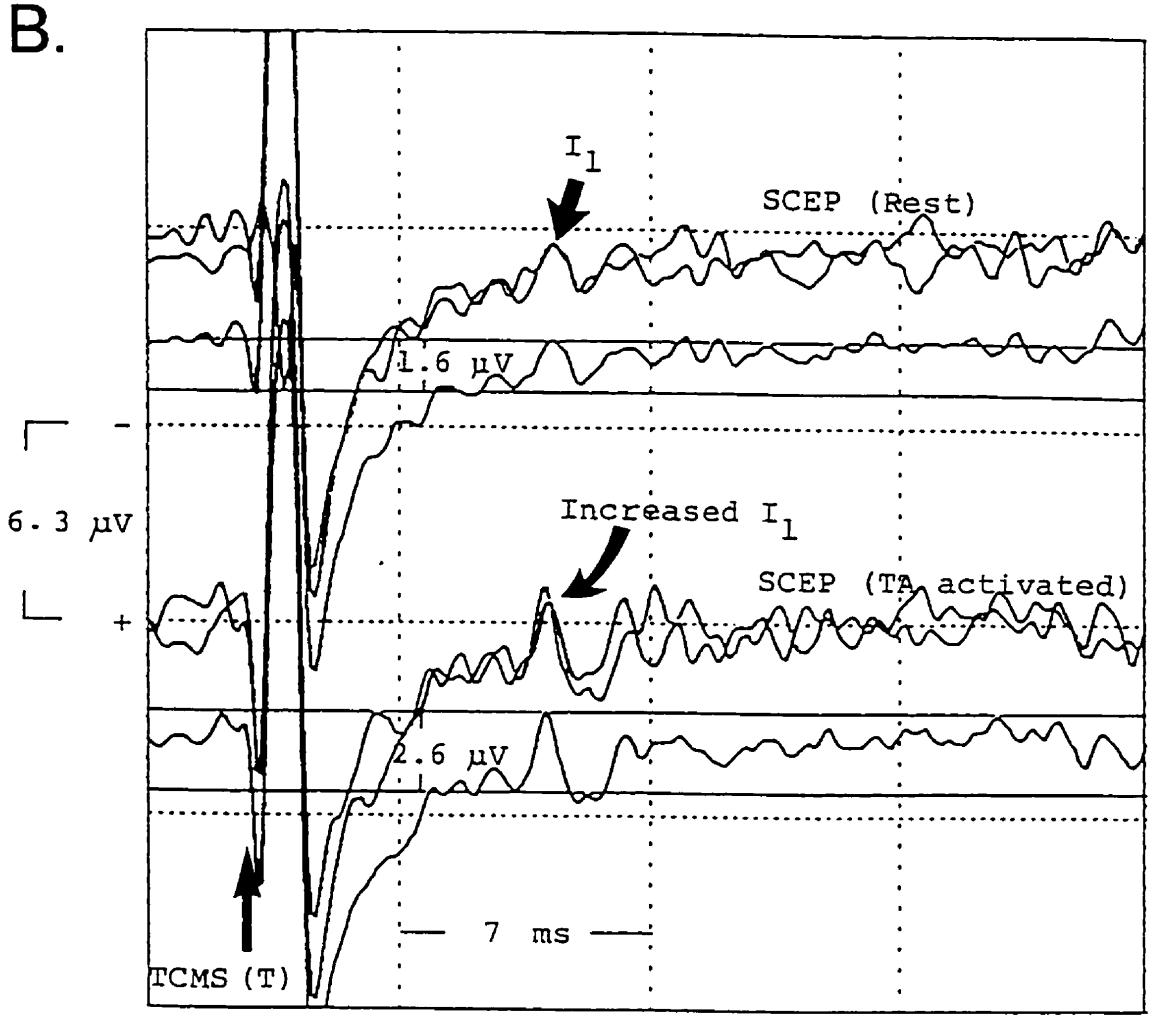


Figure 2: **A.** The effect of voluntary activation (10% of maximum voluntary contraction) of the left tibialis anterior (TA) on the spinal cord evoked response (SCEP) and muscle responses after transcranial magnetic stimulation (TCMS) using a low stimulus intensity (SCEP threshold (T)) in one subject. The stimulating coil was optimally positioned for activation of TA. The SCEP was recorded from an epidural electrode at Th8. The traces obtained at rest are designated "R" and the traces obtained during activation of TA are designated "A" as displayed on the right hand side of the figure. The SCEP contained a single wave that was verified as I_1 because higher TCMS intensities produced an earlier D wave (not shown). The reproducible I_1 was identified at T but all muscle responses were absent. During voluntary activation of TA there was facilitation of the TA and soleus (Sol) muscle responses and a concomitant increase in the I_1 wave onset-to-peak amplitude and area from 1.6 µV and 1.8 µVmsec respectively during rest to 2.6 µV and 2.46 µVmsec respectively when the same stimulus intensity was used. The responses from triceps, biceps and first dorsal interosseous (FDI) were absent at rest and during activation of the TA. Each superimposed SCEP trace is the average 5 responses and the grand average of both traces is displayed directly below them for rest and TA activated conditions. Each muscle response trace is the average of 2 responses. **B.** The same SCEP displayed on a larger scale.

B.


I_1
SCEP (Rest)
1.6 μV
Increased I_1
SCEP (TA activated)
2.6 μV
6.3 μV
−
+
7 ms
TCMS (T)

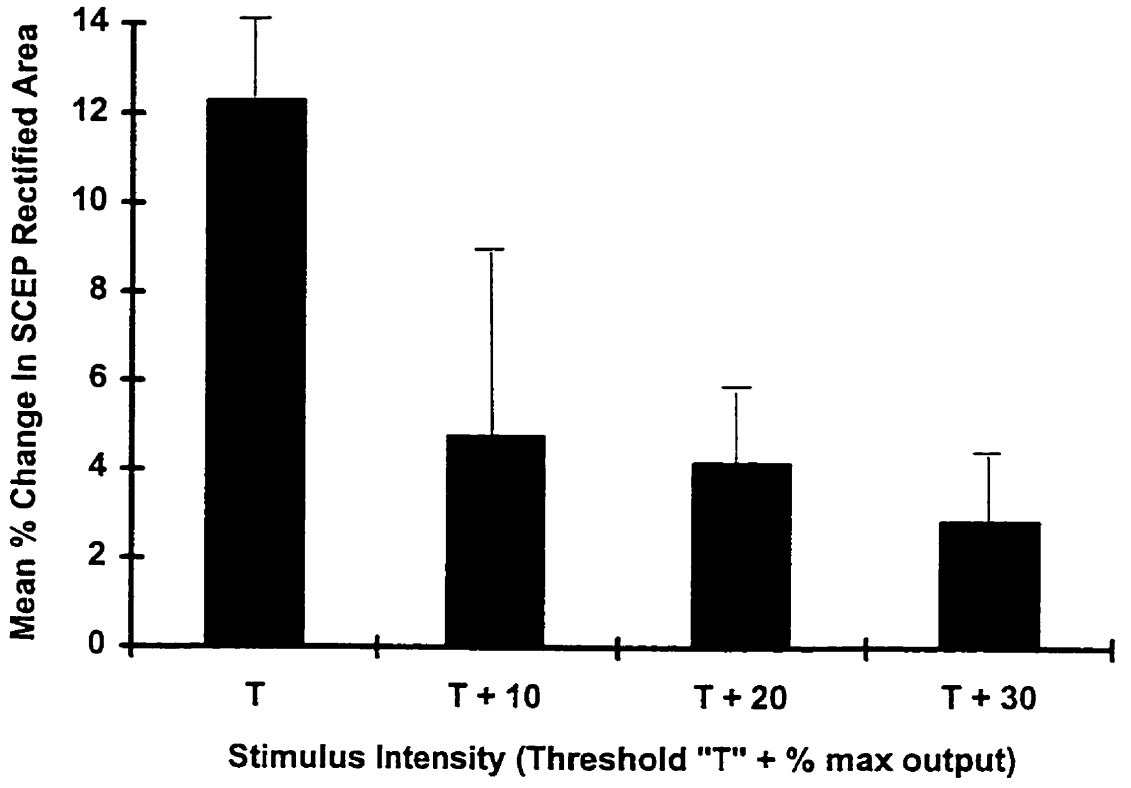


Figure 3: The mean percent change (+ 1 SE) in SCEP rectified area, between relaxed and tibialis anterior activated conditions, at various TCMS intensities. The largest mean percent change occurred at SCEP threshold (T). The variability of the percent change in SCEP rectified area increased, and the percent change in SCEP rectified area decreased when stimulus intensity increased from T to T + 10%.

contained two or less waves. During voluntary activation of TA however, the TA response at T was present in five of the seven subjects without changing the number of waves contained in the SCEP. The relationship between the number of SCEP waves and the TA response during relaxed and TA activated conditions is shown in figure 4.

Discussion

The SCEP area was significantly greater during voluntary activation of TA than at rest but only at TCMS T. This was not likely due to a change in coil position because trials were obtained during rest and TA activation in an alternating fashion so the responses contributing to each average were equally drawn from the beginning, middle and end of the experiment for each stimulus intensity. Furthermore, the natural variability in SCEP rectified area and latency was reduced by averaging six to ten responses at each stimulus intensity. Instead, this finding is useful in developing new hypotheses about corticospinal neuron excitability during voluntary activation of muscles. For example, given that the coil position was optimal for TA activation at low stimulus intensities (T), one hypothesis that may be formulated is that higher TCMS intensities, during rest, activate a greater percentage of corticospinal neurons not subserving TA and whose excitability does not change during voluntary TA activation. Another

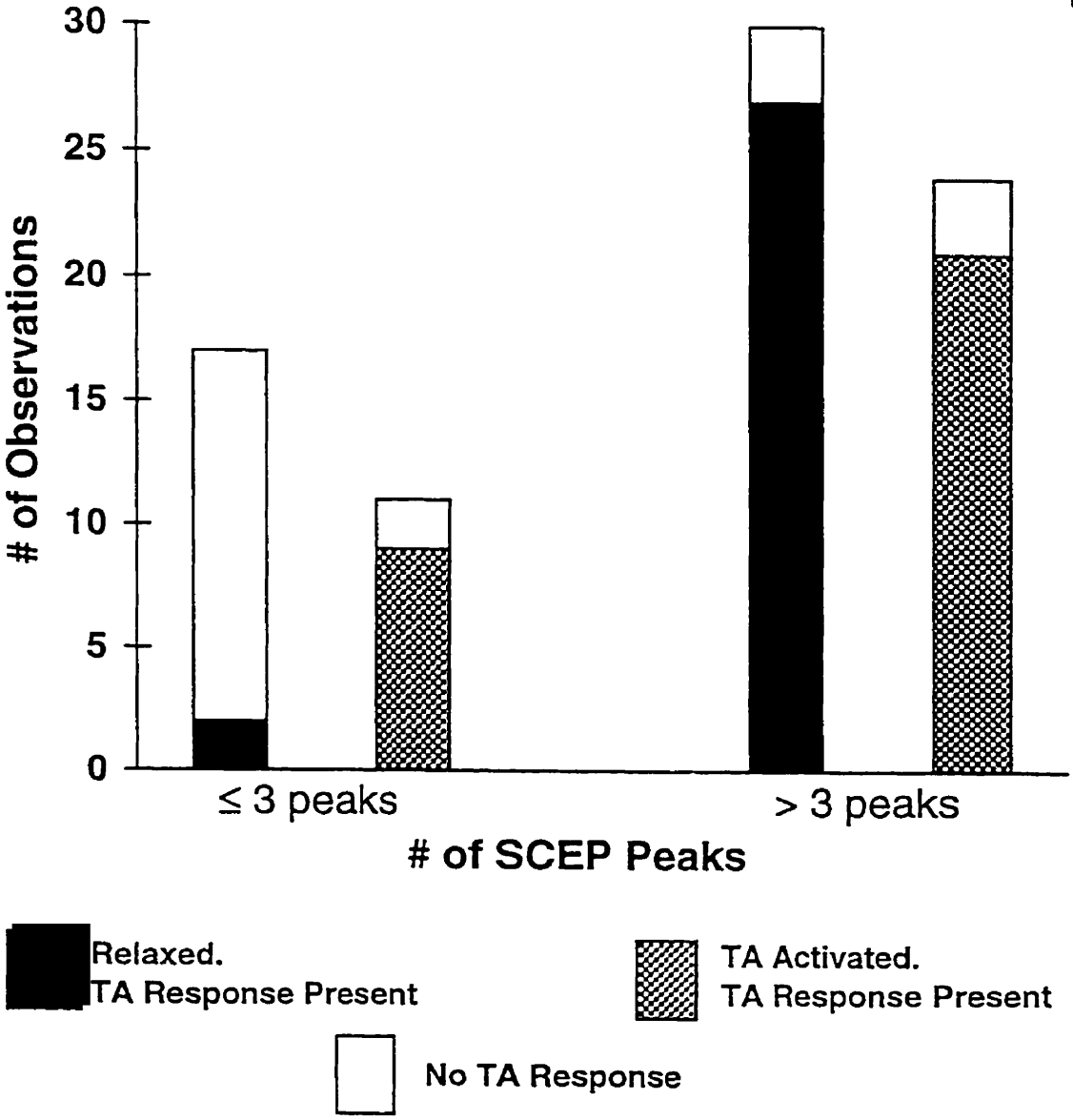


Figure 4: The number of observations where a tibialis anterior response (TA) after transcranial magnetic stimulation (TCMS) was present when the SCEP contained ≤ 3 peaks or > 3 peaks during the conditions of relaxation (Relaxed) and voluntary activation of TA (TA Activated). Only 12% (2 of 17) of observations where the SCEP had three or less peaks also had a present TA response during the relaxed condition. In contrast, during the condition of TA activation, a TA response was present in 73% (8 of 11) of observations where the SCEP had three or less peaks. When the SCEP response had more than 3 peaks, the % of observations where a TA response was present was did not differ greatly between relaxed and TA activated conditions (90 and 91% respectively).

hypothesis is that higher TCMS intensities, during rest, recruit a greater proportion of the total cortical area available for increased excitability during voluntary TA activation, so only small increments in excitability are possible during voluntary activation of TA.

The SCEP at T contained a I_1 wave in three subjects, D and I_1 waves in three subjects and I_1 and I_2 waves in one subject. The number of SCEP waves after TCMS T did not change when SCEP rectified area increased during voluntary activation. Multiple SCEP waves after a single cortical stimulus reflects repeated activation of a population of corticospinal neurons via cortico-cortical connections. Accordingly, voluntary activation of TA did not increase the number of times a group of corticospinal neurons were activated after TCMS (Patton and Amassian, 1954; Kernell and Wu, 1967) but likely increased the excitability of more corticospinal neurons so that more became synchronously active after TCMS. The excitability of corticospinal neurons may be influenced by a variety of intrinsic and extrinsic inputs. For example, the largest pyramidal cells in the motor cortex receive excitatory (and inhibitory) intrinsic input from basket and stellate cells as well as excitatory (and inhibitory) extrinsic input from the premotor cortex, primary sensory cortex and thalamus (Amassian, 1987b).

Recent experiments in a monkey showed an increase in D wave amplitude during performance of a motor task (Baker et al., 1995). After the monkey was trained to hold a precision grip between the thumb and index finger for about 1 second, SCEPs were recorded from the medullary pyramidal tract after TCMS. Only D waves were

reliably recorded. The percentage of maximum voluntary contraction in the monkey's hand muscles necessary to perform the task was not reported, but there was task-related increase of the D wave amplitude by up to 12%, which mirrored the change in mean amplitude of the EMG responses after TCMS. The results from the human study, obtained only at T (reported in this chapter) were similar to those from the monkey study. Both studies were similar in the use of low TCMS intensities and a sustained voluntary contraction. In the monkey experiment the D wave onset-to-peak amplitude after TCMS increased the most during the hold period so it was not surprising to see a significant increase in SCEP area after TCMS when human subjects were holding a 10% maximum voluntary contraction of TA. Our findings favour the facilitation of I waves since 4 of the 7 subjects had only I waves present at T. Other human studies showed an increase in the amplitude of muscle responses after TCMS during a period of presumed increased cortical excitability after a ballistic muscle contraction (Mills and Kimiskidis, 1996).

At TCMS intensities above T, SCEP rectified area did not significantly increase during voluntary activation of TA, compared to rest. In contrast to the findings obtained at T, the SCEP rectified area at higher TCMS intensities was decreased or unchanged in some subjects and increased in others. Accordingly, another hypothesis is that higher TCMS intensities activated a larger cortical area with a different proportion of inhibitory and excitatory intrinsic connections to corticospinal neurons, than lower TCMS intensities.

Failure to detect a significant increase in SCEP rectified area at higher TCMS intensities suggests spinal motoneuron excitability must also play a role in facilitation of muscle responses during a sustained voluntary contraction. Furthermore, it is unlikely that the increased SCEP rectified area observed at TCMS T could totally account for the degree of TA facilitation observed at T. For example, during relaxation, the leg muscle responses were usually absent if the SCEP had three or less peaks. The TA response after TCMS, during the relaxed condition, was present in only 12% of observations when the SCEP had three or less peaks. In contrast, as few as one or two SCEP waves were sufficient to evoke a response from the TA during voluntary activation of TA in six of the seven subjects. This supports previous work which has shown that, during voluntary muscle activation, depolarization of some alpha motoneurons can occur after the arrival of the I_1 wave instead of after the summation effects of later I waves (Day et al., 1987).

Voluntary muscle contraction of TA facilitated other muscles in the upper and lower extremities in addition to TA. Previous investigators have shown that the excitability of spinal motoneurons at multi-segmental levels is increased during facilitation (Pereon et al., 1995; Delwaide and Toulouse, 1981). Two distinct mechanisms to explain this phenomenon have been proposed; 1) moderate motor facilitation from a supraspinal origin, and 2) a more marked facilitation resulting from proprioceptive afferent impulses originating from the target muscle contraction (TA) that are transmitted to supraspinal relays and then descend in spinal facilitatory pathways. It is also possible that spinal

motoneuron excitability at multi-segmental levels was increased because of activation of muscles other than the TA despite our best efforts to ensure they were relaxed.

Alpha motoneuron excitability is dependent on suprasegmental inputs (especially from the corticospinal, rubrospinal and reticulospinal systems), segmental inputs (especially from muscle spindles and Golgi tendon organs) and the level of presynaptic inhibition of these systems (Amassian et al., 1987b). The proximity of the alpha motoneuron membrane potential to threshold for depolarization, and its membrane conductance, will determine whether the it will fire following a given stimulus (Amassian et al. 1987b). More alpha motoneurons were depolarized during voluntary activation of TA, compared to rest, to account for the facilitation of muscle responses after TCMS. During voluntary activation of TA it is likely that a combination of effects occurred to depolarize more alpha motoneurons after TCMS. For example, increased tonic discharge of corticospinal neurons may have directly or indirectly (through facilitory interneurons or externally through muscle spindle afference) raised alpha motoneuron excitability during voluntary activation of TA. Superimposed on this raised alpha motoneuron excitability was the arrival of a SCEP, after TCMS, which had a larger rectified area (due to increased cortical excitability) that would result in increased EPSPs at alpha motoneurons.

In summary, increased excitability of spinal motoneurons and corticospinal neurons may facilitate muscle responses during voluntary activation. Increased excitability of

corticospinal neurons (indicated by increased SCEP rectified area) was observed only at T and generated new hypotheses related to corticospinal neuron excitability during voluntary muscle contraction at different TCMS intensities.

CHAPTER VIII

Conclusions and Future Directions

Conclusions

SBS recruited muscles in the upper extremities at lower SBS intensities and to a larger extent than muscles in the lower extremities. The following possibilities should be considered as a way of explaining this finding.

1. Excitation of a greater number of descending fibres that send projections to spinal motoneurons in the cervical spinal cord than the lumbosacral spinal cord. For example, the rubrospinal and medial vestibulospinal pathways make monosynaptic connections to alpha motoneurons in the cervical spinal cord but do not send any projections to the lumbosacral cord. Furthermore, the reticulospinal pathways send more direct projections to the cervical spinal cord than the lumbosacral spinal cord (Nathan et al., 1996) and the corticospinal pathways have more monosynaptic connections to alpha motoneurons in the cervical spinal cord than the lumbosacral spinal cord (Bernhard and Bohm, 1954; Phillips and Porter, 1964). The fact that vestibulospinal projections excite mainly extensor muscles may explain why triceps was particularly responsive to SBS.

2. Ineffective activation of lumbosacral spinal motoneurons. The timing of descending volleys on spinal motoneurons for the arms may be better

than that for the hands which may be better than that for the legs. For example, the fibres that have an effect on lumbosacral spinal motoneuron excitability may reside in corticospinal, vestibulospinal, reticulospinal, raphespinal, coerulospinal, interstitiospinal or propriospinal pathways. These pathways, and the fibres they contain, have different conduction velocities so by the time the SCEP arrives at the lumbosacral spinal cord it may have a lower amplitude than the SCEP at the cervical spinal cord because of temporal dispersion, thereby making it less effective in alpha motoneuron depolarization. Another possibility is that depolarization of lumbosacral alpha motoneurons is contingent on a SCEP that contains more than 3 peaks but the cervical motoneurons need only a single peak.

It is also possible that stimulus current spread to the cervical spinal cord raised the membrane potential of alpha motoneurons to subthreshold levels such that a descending volley occurring 1 or 2 ms later would depolarized it by way of temporal summation (stimulus current spread to lumbosacral spinal cord does not occur because the distance between the stimulating electrodes and the lumbosacral spinal cord is too great). This was unlikely to occur because axons closer to the stimulator should have lower thresholds than the alpha motoneuron membrane (except for the initial segment) in the cervical spinal cord which should result in a

decrease in the latency of the descending SCEP after SBS, but the descending SCEP latency did not decrease (see Chapter 5).

3. Activation of more corticospinal fibres projecting to the cervical spinal cord than the lumbosacral spinal cord. The horizontal orientation of the anode and cathode over the back of the skull may have preferentially activated the corticospinal tract at its decussation in the medulla because, at this location, it lies approximately parallel to the current flow. The fibres to the cervical spinal cord may have been selectively activated at lower stimulus intensities because they are located more rostrally (closer to the stimulating electrodes).

4. Antidromic activation of dorsal column fibres increased the excitability of alpha motoneurons to subthreshold levels in the cervical but not the lumbosacral spinal cord. The dorsal column nuclei do not directly project to alpha motoneurons but may be able to change their excitability through interneurons in the spinal grey. It is possible that SBS preferentially activated the cuneate nucleus (that projects to the cervical spinal grey) more than the gracile nucleus (that projects to the lumbosacral spinal grey) since the cuneate nucleus is positioned more rostral in the medulla and closer to the stimulating electrodes than the gracile nucleus. Another possibility is that the dorsal column nuclei or

dorsal column fibres were activated uniformly for the upper and lower extremities but, because of the longer distance from the stimulating electrodes to the lumbosacral spinal cord than the cervical spinal cord and the slower conduction velocity in the dorsal columns than in motor pathways, the timing of the descending dorsal column volley to the lumbosacral spinal cord arrived too late to have an effect on alpha motoneurons. Arguments against dorsal column involvement in alpha motoneuron excitability come from animal studies that showed the peripheral motor responses, after widespread spinal cord stimulation, were insensitive to the functional status of the dorsal columns (Owen et al., 1989).

In any case, SBS likely activated multiple descending pathways and their propriospinal connections so the effect, both temporally and spatially, on the excitability of spinal motoneurons is likely to be very complex and cannot be resolved here. Nevertheless, the net effect was excitation of alpha motoneurons supplying arm muscles, more than hand muscles, more than leg muscles.

A latency decrease in muscles of the upper extremities, but not lower extremities, occurred when SBS increased within the lower ranges of SBS intensity. This latency decrease could not be attributed to stimulus current

spread to cervical nerve roots. The following possibilities should be considered to account for this finding.

1. SBS recruited proportionally more alpha motoneurons in the cervical spinal cord than in the lumbosacral spinal cord (see Chapter 3). As such, when SBS intensity increased, the larger spinal motoneurons with faster peripheral axons supplying muscles in the upper extremity may have been recruited resulting in shorter latencies to those muscles. This effect was not seen in the lower extremities because fewer alpha motoneurons were recruited even at high SBS intensities. It is also possible that alpha motoneurons in the cervical spinal cord were weakly activated by mainly polysynaptic connections at threshold, but at higher SBS intensities a stronger combination of poly- and monosynaptic connections were activated with the monosynaptic connections resulting in muscle responses with a shorter latencies. In contrast, the lumbosacral alpha motoneurons were only activated at higher SBS intensities by relatively fewer monosynaptic connections.

2. Stimulus current spread resulting in depolarization of more caudal sites in the central nervous system was unlikely because the SCEP latency did not greatly change as SBS increased (see Chapter 5). Stimulus current spread directly to the initial segment of the alpha motoneuron axons

supplying biceps and triceps was also unlikely at lower stimulus intensities because voluntary activation of triceps increased the amplitude and decreased the latency of the triceps response after SBS suggesting the triceps muscle response was dependent on presynaptic excitation of triceps alpha motoneurons.

3. Alpha motoneuron excitability may have been increased to subthreshold levels that would not have been detected on background EMG. SBS is uncomfortable, so the subjects may have become more anxious as the experiment progressed thereby increasing the amount of background subthreshold excitatory drive on alpha motoneurons through corticospinal as well as the medial, lateral and bulbospinal brainstem pathways. Increases in alpha motoneuron excitability would result in a shorter time course for alpha motoneuron depolarization following the arrival of a descending volley after SBS, thereby resulting in a muscle response with a shorter latency. It is possible that leg muscle latencies did not decrease because the excitatory drive to raise alpha motoneuron excitability was greater in the cervical spinal cord than the lumbosacral spinal cord. This may be due to a greater number of direct connections to the cervical spinal cord from the corticospinal, rubrospinal, reticulospinal, vestibulospinal and tectospinal pathways and possibly the coerulospinal, sub-coerulospinal, raphespinal and interstitiospinal

pathways, all of which may affect alpha motoneuron excitability. Another possibility is that the subjects, through all or some of these pathways, were sub-consciously increasing the excitability of the alpha motoneurons supplying muscles in the upper extremity more than those in the lower extremity.

Peripheral afferent input to the spinal cord (ie. from muscle spindles, golgi tendon organs) can also affect the excitability of alpha motoneurons. For example, stretching a muscle can increase muscle spindle afference which in turn increases the excitability of alpha motoneurons. This rationale does not explain why the excitability of alpha motoneurons supplying the leg muscles, and in particular quadriceps and soleus which receive strong input from muscle spindles, did not change unless the spindle afference from the lower extremities was less than that from the upper extremities.

SBS always recruited triceps earlier and to larger extent than FDI. A number of possibilities should be considered to explain this finding. Most of the arguments described above may be used to explain why alpha motoneurons supplying triceps were recruited earlier and to a larger extent than those supplying FDI (ie. more descending projections, better timing of descending volley and less temporal dispersion of SCEP, more stimulus current spread to alpha

motoneurons, activation of pathways that preferentially activate triceps, preferential activation of fibres projecting to triceps within a tract, increased central and/or peripheral drive to triceps motoneurons). Temporal dispersion of the descending volley over the distance between the alpha motoneuron pool supplying triceps at C6/7 and that supplying FDI at C8/Th1 is unlikely because the distance between the two levels is too short. The distance between descending fibres in the medulla that project to triceps and FDI and the difference in their orientation at this level is negligible so preferential excitation of fibres projecting to triceps motoneurons, within a tract, is unlikely. Stimulus current spread to triceps alpha motoneurons is possible, but unlikely, because the excitability of triceps motoneurons depends on presynaptic excitation. It is possible that triceps alpha motoneurons received more presynaptic excitation from increased efferent input from supraspinal centres as well as increased peripheral afference that raised its excitability to subthreshold levels thereby increasing their chances of firing but the leg muscles, that also have strong spinal reflexes, were only weakly activated by SBS suggesting raised excitability of triceps motoneurons plays a minor role. Instead, it is likely that SBS activated other motor pathways in addition to the corticospinal pathways. Descending motor pathways that have strong projections to proximal arm muscles include the medial brainstem pathways. The medial brainstem pathways (reticulospinal, vestibulospinal and interstitiospinal pathways) are involved in synergistic movements of proximal arm muscles (like triceps), as

well as in orienting movements involving axial muscles. In contrast, the rubrospinal pathway and the corticospinal pathway are mainly involved in movements of the distal muscles of the upper extremity. The complexity of simultaneous activation of all descending motor pathways (corticospinal, lateral brainstem, medial brainstem and bulbospinal pathways) makes interpretation of the data difficult, but the result is earlier and more recruitment of triceps than FDI alpha motoneurons.

The medial brainstem pathways are mainly postural so it was expected that activation of these pathways after SBS would activate muscles in the lower extremities to a larger extent than they did. Weak activation of lower extremity muscles after SBS may be the result of fewer direct connections from all motor pathways to alpha motoneurons in the lumbosacral spinal cord. It is also possible that the stimulus was inappropriate for activation of alpha motoneurons in the lower extremities. For example, the TA muscle responses after TCMS were usually contingent on a SCEP containing more than 3 peaks, but the SCEP after SBS had only a single peak. It is likely that the lumbosacral spinal motoneurons require a descending input that is more sophisticated than that created by a square wave stimulus pulse grossly applied to the base of the skull. Nevertheless, the following conclusions can be made.

I. SBS activated triceps earlier and to a larger extent than FDI which is the

opposite to what happens after TCMS. These results were not contaminated by stimulus current spread to nerve roots. Accordingly, SBS activated descending projections that resulted in more excitation of triceps alpha motoneurons than FDI alpha motoneurons.

II. The SCEP after TCMS and SBS was different at stimulus intensities above T. The SCEP after TCMS resulted from direct and indirect activation of corticospinal cells while that after SBS resulted from activation of long tracts. The waves after TCMS were similar to the D and I waves previously recorded from the spinal cord of anaesthetized monkeys after surface anodal stimulation of the brain (Patton and Amassian, 1954). The D and I waves after TCMS were temporally coded to allow for efficient motoneuron depolarization in the lumbo-sacral spinal cord by temporal summation. In contrast, SBS activated long tracts resulting in a single wave of depolarization that was less effective than TCMS in activating leg muscles.

III. Increased excitability of corticospinal neurons during voluntary activation of TA (indicated by increased SCEP rectified area) was observed at T but not at TCMS intensities above T. This suggested muscle facilitation was related to increased excitability in some corticospinal neurons (that was detected at T) as well as increased excitability in spinal

motoneurons.

Future Directions

Collision of the descending volley after TCMS or SBS with an ascending volley after dorsal spinal cord stimulation may help determine whether the SCEP after SBS is conducted in the ventral spinal cord. Shimoji demonstrated that dorsal spinal cord stimulation (several times SCEP threshold) activated only the dorsal half of the spinal cord including the dorsolateral corticospinal tract (Shimoji et al., 1995). The DCS electrode contains four leads so two may be used for dorsal spinal cord stimulation and two for recording the SCEP.

SBS studies in patients that have degeneration in specific descending pathways may help elucidate the pathways activated after SBS. In these patients, the pattern of muscle activation should be studied in muscles that receive strong excitation from the corticospinal pathways as well as those that receive weak excitation from the corticospinal pathways.

Facilitation studies should be repeated during tasks demanding fine motor control. Baker demonstrated an increased SCEP amplitude recorded from the medulla in a monkey performing a high precision hand task (Baker et al., 1994).

A similar experiment could be designed in human subjects with DCS electrodes positioned above C7 in the cervical spine so that changes in motor cortical outflow to hand muscles may be observed. The time course of SCEP facilitation as it relates to the planning and execution of the task, the selective effects on D and/or I waves and the effect motor learning has on SCEP facilitation may help improve our understanding of motor control.

Repetitive, high frequency TCMS and TCES techniques have been recently used intraoperatively to monitor motor pathways (Kalkman et al., 1995). Muscle responses that are depressed or absent after a single stimulus are readily evoked after repetitive stimulation presumably due to the artificial replacement of I waves that are lost because of anaesthesia. The SCEP after SBS is minimally affected by anaesthesia and SBS preferentially activates different muscles than TCMS. Accordingly, repetitive SBS may be a useful compliment to TCMS in intraoperatively monitoring motor pathways.

Coil orientation may change the pattern of D and I wave activation (Amassian et al., 1990). If the coil is held tangential to the scalp then cortico-cortical connections lying parallel to the current flow are preferentially activated and I waves should be facilitated. In contrast, if the coil is held on a sagittal plane then the majority of corticospinal neurons, their apical dendrites and their descending axons should lie parallel to the current flow and D waves should be

facilitated. The effect of coil position on the D and I wave amplitude, pattern of activation of D and I waves and the amplitude and latency of muscle responses may help determine the neural structures activated by TCMS at various coil positions and orientations. This knowledge is essential for accurate interpretation of results if TCMS is to be used as a way of investigating the function of central motor pathways in health and disease.

APPENDIX I

Raw SCEP Amplitude and Latency Data

After SBS and TCMS

APPENDIX I: Raw SCEP Data

SBS Amplitude Data

SUBJECT INFO	SBS INTENSITY	SCEP O - P (μV)	Waveform P-T (μV)	RMS	AREA	BICEPS P-P (μV)	TRICEPS P-P (μV)	FDI P-P (μV)	TA P-P (μV)	SOL P-P (μV)
ID: BB	T	2.9	0.9	4.2	1.6	6.0	11.0			
Age:	T + 7.5	18.8	16.4	10.3	10.4	17.0	34.0			
Sex	T + 15	34.4	34.4	20.8	22.9	864.0	204.0	17.0		4.0
	T + 22.5	48.0	46.0	29.7	30.1	2730.0	552.0	62.0	5.6	6.0
ID: AM	T	7.0	5.0	9.5	4.1					
Age:	T + 7.5	24.0	20.0	22.1	14.5	17.0	21.0	36.0		
Sex:	T + 15	39.0	39.0	32.1	25.6	126.0	44.0	105.0		
	T + 22.5	50.0	40.0	51.5	28.8	2700.0	780.0	1020.0	24.0	7.0
ID: BL	T	2.5	2.5	6.6	0.8					
Age:	T + 7.5	6.0	6.4	11.2	4.2	16.0	16.0	16.0		
Sex:	T + 15	11.0	17.0	12.6	13.6	264.0	184.0	28.0		
	T + 22.5	18.1	24.2	22.5	28.8	720.0	381.0	172.0		
ID: M	T	6.4	18.0	8.4	17.2	16.0	42.0			
Age:	T + 7.5	14.0	32.0	14.2	32.0	183.0	120.0			
Sex:	T + 15	22.0	43.0	20.1	45.0	400.0	318.0			
	T + 22.5	26.4	54.0	25.1	61.0	640.0	510.0			
ID: IA	T	0.6	0.9	6.5	1.2		12.0			
Age:	T + 7.5	2.1	4.9	10.8	8.3		12.0			
Sex:	T + 15	7.1	19.4	11.8	17.4	87.0	42.0			
	T + 22.5	23.0	51.0	32.3	43.7	1403.0	1070.0	56.0		6.0
ID: C	T	4.0	5.1	6.8	4.7		15.0			
Age:	T + 7.5	10.1	14.6	13.0	12.9	12.0	20.0			
Sex:	T + 15	19.3	28.0	17.8	22.1	101.0	79.0	12.0		
	T + 22.5	38.0	40.3	29.9	41.0	576.0	487.0	51.0		6.0

APPENDIX I: Raw SCEP Data

SBS Latency Data

SUBJECT INFO	SBS INTENSITY	SCEP Waveform		BICEPS	TRICEPS	FDI	TA	SOL
		Onset (ms)	Peak (ms)	Onset (ms)	Onset (ms)	Onset (ms)	Onset (ms)	Onset (ms)
ID: BB	T	3.2	4.2	9.6	11.3			
Age:	T + 7.5	3.4	4.2	9.6	10.6			
Sex	T + 15	3.4	4.1	7.0	8.2	17.6		40.4
	T + 22.5	3.4	4.1	7.0	8.2	19.6	38.2	40.1
ID: AM	T	3.1	3.8					
Age:	T + 7.5	3.1	3.8	8.2	12.2	17.4		
Sex:	T + 15	3.1	3.8	6.3	12.4	17.4		
	T + 22.5	3.1	3.8	6.0	5.6	16.9	29.9	30.7
ID: BL	T	4.2	4.9					
Age:	T + 7.5	4.2	4.9	8.2	11.1	23.2		
Sex:	T + 15	4.3	4.9	6.6	9.8	19.9		
	T + 22.5	4.2	4.8	6.5	7.3	16.3		
ID: M	T	4.1	4.9	10.6	10.3			
Age:	T + 7.5	4.2	4.9	8.7	10.4			
Sex:	T + 15	4.1	4.9	8.8	11.2			
	T + 22.5	4.1	4.9	8.7	11.1			
ID: IA	T	5.0	5.8		9.4			
Age:	T + 7.5	4.3	0.4		8.4			
Sex:	T + 15	4.4	4.9	8.1	8			
	T + 22.5	4.1	4.8	5.9	5.9	20.4		35.3
ID: C	T	3.3	4.1		10.2			
Age:	T + 7.5	3.3	4.0	8.7	10.2			
Sex:	T + 15	3.3	4.0	8.0	9.8	22.9		
	T + 22.5	3.3	4.0	6.0	7.7	22.6		

APPENDIX I: Raw SCEP Data

TCMS SCEP Amplitude Data

SUBJECT INFO	TCMS INTENSITY	D Wave		I_1 Wave		I_2 Wave		I_3 Wave		I_4 Wave		SCEP Area
		O-P (uV)	P-T (uV)	O-P (uV)	P-T (uV)	O-P (uV)	P-T (uV)	O-P (uV)	P-T (uV)	O-P (uV)	P-T (uV)	(uV ms)
ID: BB	T			3.8	6.5	3.1	1.0					5.8
Age:	T + 10	0.8	0.8	6.4	10.6	5.4	1.4	3.4	4.4	3.2	2.8	13.8
Sex:	T + 20	0.8	1.4	7.4	13.4	8.0	4.0	8.0	11.2	8.2	7.0	19.5
	T + 30	1.6	2.0	7.0	13.6	10.8	7.0	7.4	8.4	9.2	12.6	27.4
ID: AM	T	2.3	2.6	1.9	1.1	0.6	1.4					1.9
Age:	T + 10	2.6	4.4	2.0	0.7	2.9	3.6	0.9	1.5			7.4
Sex:	T + 20	3.7	5.9	2.2	1.8	1.8	2.6	2.2	2.2	1.5	1.7	13.6
	T + 30	5.1	6.3	3.3	2.6	4.8	5.0	4.1	3.0	8.9	9.2	23.7
ID: BL	T			0.6	0.8							0.7
Age:	T + 10	0.7	1.0	1.7	1.9	0.8	0.4					2.2
Sex:	T + 20			1.7	2.3	1.5	0.4	0.8	1.0			3.3
	T + 30	1.5	1.7	2.2	2.3	2.1	1.2	1.2	1.7			5.1
ID: C	T			1.6	0.8							0.6
Age:	T + 10	2.2	2.4	1.7	2.7							4.5
Sex:	T + 20	3.4	3.3	2.2	4.7							6.0
	T + 30	5.6	4.5	2.7	6.4	3.0	0.4	1.6	0.4			11.3
ID: IA	T			6.4	6.4							2.2
Age:	T + 10	3.2	5.0	5.9	6.4	4.5	2.3	5.0	5.4			15.3
Sex:	T + 20	4.1	4.1	7.3	7.7	6.4	2.7	3.2	4.5	10.0	6.4	21.1
	T + 30	5.7	4.6	7.1	8.2	5.9	4.0	7.1	7.4	10.0	8.1	27.4
ID: M	T	2.3	2.3	2.7	2.0							3.1
Age:	T + 10	2.6	2.4	2.5	2.5	2.0	0.8					9.0
Sex:	T + 20	2.9	2.5	2.1	3.1	3.4	0.1	5.1	11.1			20.8
	T + 30	4.0	3.3	2.3	4.6	4.0	0.5	5.3	8.0			21.0
ID: HZ	T			2.6	1.4							3.5
Age:	T + 10	0.8	5.0	5.6	2.4							5.7
Sex:	T + 20	1.0	6.8	7.0	3.6	2.2	3.0	3.4	1.2			11.1
	T + 30	0.8	7.0	7.6	5.6	2.8	4.0	3.8	5.0	4.4	1.2	21.2
ID: EH	T			1.1	1.0							0.7
Age:	T + 10			1.5	1.4							1.0
Sex:	T + 20	0.3	1.0	2.0	1.8	0.5	0.5	1.0	0.6			3.3
	T + 30	0.2	0.8	1.3	1.6	0.3	0.8	1.6	1.0			3.6
ID: SS	T	0.3	0.3	1.4	1.4							2.5
Age:	T + 10	0.4	0.4	2.4	2.7	0.9	0.7	3.1	2.7			5.8
Sex:	T + 20	0.3	1.3	4.5	4.2	0.8	1.2	4.6	2.9	0.6	1.3	9.1
	T + 30	0.9	1.2	3.5	3.9	2.0	0.2	1.2	1.8	3.2	2.4	8.3
ID: TA	T	0.3	0.5	1.4	2.0							1.9
Age:	T + 10	1.2	1.3	2.7	3.3	1.6	0.9	2.1	2.1			5.7
Sex:	T + 20	2.6	2.1	4.1	6.0	3.8	0.8	2.9	3.5			9.3
	T + 30	4.1	3.7	3.7	6.7	4.8	2.2	3.4	2.8			10.9

O: Onset ; T: Trough ; P: Peak

APPENDIX I: Raw SCEP Data

TCMS SCEP Latency Data

SUBJECT INFO	TCMS INTENSITY	D Wave		I_1 Wave		I_2 Wave		I_3 Wave		I_4 Wave	
		Onset (ms)	Peak (ms)	Onset (ms)	Peak (ms)	Onset (ms)	Peak (ms)	Onset (ms)	Peak (ms)	Onset (ms)	Peak (ms)
ID: BB	T			6.8	7.6	8.3	9.3				
Age:	T + 10	5.6	6.0	6.8	7.4	8.2	9.3	9.8	10.6	11.5	12.5
Sex:	T + 20	5.7	6.3	6.8	7.6	8.3	9.2	9.8	10.6	11.5	12.3
	T + 30	5.4	6.2	6.8	7.4	8.2	9.2	9.8	10.5	11.4	12.3
ID: AM	T	6.7	7.3	8.0	8.9	9.7	10.6				
Age:	T + 10	6.4	7.3	8.1	8.9	9.4	10.2	11.2	11.9		
Sex:	T + 20	6.2	7.2	8.0	8.9	9.5	10.3	11.3	12.0	12.9	14.3
	T + 30	6.4	7.1	8.0	8.9	9.5	10.4	11.3	11.9	12.8	14.0
ID: BL	T			7.7	8.4						
Age:	T + 10	6.4	7.0	7.6	8.2	9.4	10.1				
Sex:	T + 20			7.6	8.2	9.2	10.3	10.8	11.8		
	T + 30	5.3	6.6	7.6	8.3	9.2	10.0	10.9	11.8		
ID: C	T			7.2	8.0						
Age:	T + 10	5.4	6.5	7.1	7.9						
Sex:	T + 20	5.3	6.2	7.1	7.7						
	T + 30	5.5	6.6	7.1	7.7	8.7	9.7	10.0	10.6		
ID: IA	T			7.5	8.5						
Age:	T + 10	6.0	6.9	7.5	8.3	9.1	10.0	10.6	11.3		
Sex:	T + 20	6.1	6.9	7.5	8.2	9.0	10.0	10.5	11.3	12.3	13.2
	T + 30	6.2	7.1	7.7	8.4	9.2	10.1	10.9	11.7	12.4	13.2
ID: M	T	6.9	7.7	8.2	9.5						
Age:	T + 10	6.8	7.7	8.3	9.3	9.9	10.9				
Sex:	T + 20	6.8	7.7	8.4	9.1	9.9	10.9	11.2	12.1		
	T + 30	6.8	7.6	8.3	8.9	9.8	10.7	11.1	12.0		
ID: HZ	T			8.9	10.1						
Age:	T + 10	7.4	8.0	8.9	9.8						
Sex:	T + 20	7.4	8.0	8.6	9.6	10.5	11.2	11.8	12.8		
	T + 30	6.8	7.7	8.6	9.5	10.4	10.9	11.7	12.5	13.3	14.2
ID: EH	T			7.6	8.8						
Age:	T + 10			7.8	8.4						
Sex:	T + 20	6.1	7.0	7.7	8.4	9.6	10.1	10.7	11.7		
	T + 30	6.1	7.0	7.7	8.4	9.4	10.1	10.8	11.9		
ID: SS	T	7.9	8.5	9.2	10.3						
Age:	T + 10	7.77	8.5	9.3	10.1	10.9	11.7	12.5	13.3		
Sex:	T + 20	7.3	8.1	9.2	10.2	11.2	11.7	12.3	13.0	14.3	15.0
	T + 30	7.6	8.2	9.1	10.1	10.8	11.6	12.3	13.1	14.0	15.0
ID: TA	T	6.3	7.0	7.9	8.5						
Age:	T + 10	6.5	7.2	7.8	8.6	9.4	10.3	10.8	11.7		
Sex:	T + 20	6.3	7.1	7.8	8.4	9.3	10.2	10.8	11.4		
	T + 30	6.2	7.1	7.8	8.3	9.3	10.2	10.7	11.6		

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IMAGE EVALUATION
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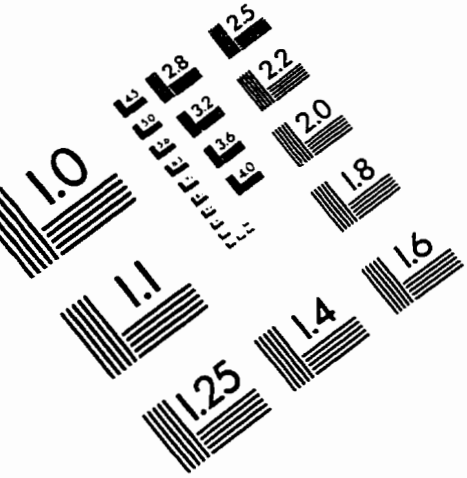

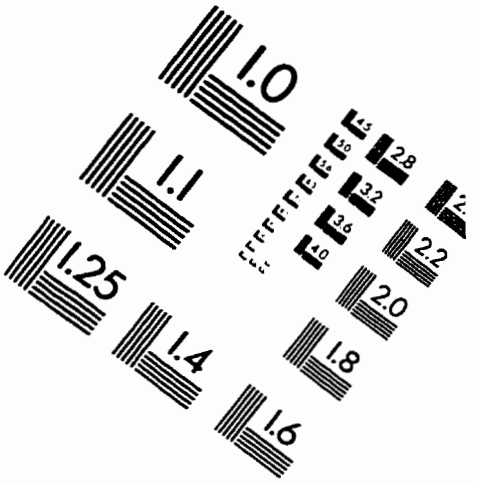

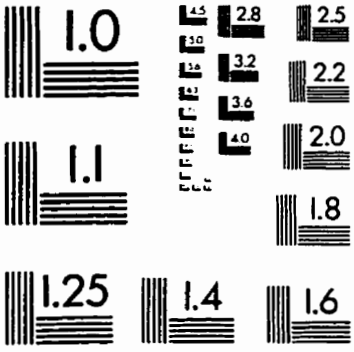

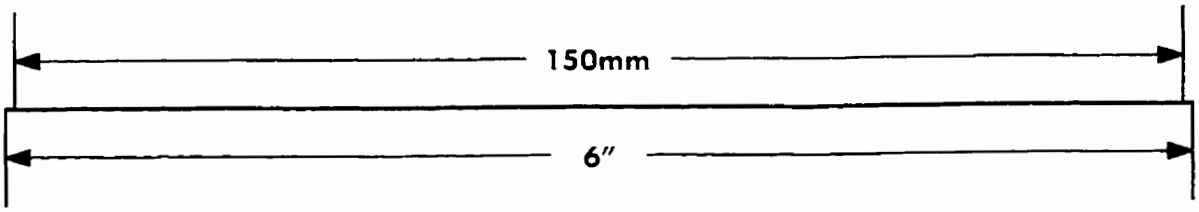

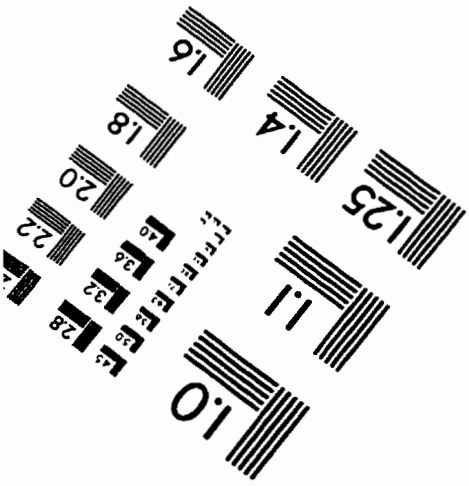

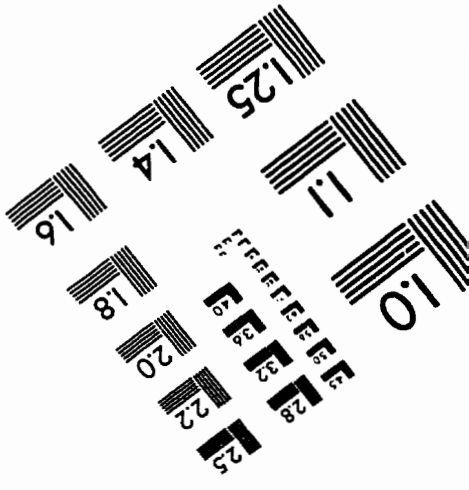

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