Modelling magnetic coil excitation of human cerebral cortex with a peripheral nerve immersed in a brain-shaped volume conductor: the significance of fiber bending in excitation

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Summary   To help elucidate some basic principles of magnetic coil (MC) excitation of cerebral cortex, a model system was devised in which mammalian phrenic nerve, or amphibian sciatic nerve with its branches was suspended in appropriate Ringer's solution in a human brain-shaped volume conductor, an inverted plastic skull. The nerve was recorded monophasically out of the volume conductor. The site of nerve excitation by the MC was identified by finding where along the nerve a bipolar electrical stimulus yielded a similar action potential latency. MC excitation of hand-related corticospinal (CT) neurons was modelled by giving the distal end of nerve attached to the lateral skull an initial radial (perpendicular) trajectory, with subsequent bends towards the base and posterior part of the skull; this nerve was optimally excited by a laterally placed figure 8 or round MC when the induced electric field led to outward membrane current at the initial bend. By contrast, nerve given a trajectory modelling CT neurons related to the foot was optimally excited when the coil windings were across the midline, but again when membrane current flowed outward at the first bend. Corticocortical fibers were modelled by placing the nerve in the anteroposterior axis lateral to the midline; with the round MC vertex-tangentially orientated, optimal excitation occurred at the bend nearest the interaural line, i.e., near the peak electric field. The findings emphasize the importance of orientation and direction of current in the MC and fiber bends in determining nerve excitation. The findings in the peripheral nerve-skull model help explain (1) why lateral and vertex-tangentially orientated MCs preferentially excite arm-related CT neurons directly and indirectly (through corticocortical fibers), respectively, and (2) why the MC orientations for optimally exciting directly arm and leg-related CT neurons differ.

Key words: Magnetic stimulation; Nerve excitation; Brain model; Corticospinal

Following the introduction in humans of electrical (Merton and Morton 1980) and magnetic coil transcranial stimulation (Barker et al. 1985), major differences in the motor responses to these two kinds of stimulation were described. These included: (1) Motor responses to magnetic coil (MC) stimulation were widespread when the coil was conventionally applied tangentially at the vertex (Barker et al. 1987). Subsequently, using "edge" stimulation by the round MC (Amassian et al. 1987a), or two edges in the twin coil configuration, focal responses, e.g., predominantly of a single digit could be elicited (Amassian et al. 1988, 1989a). (2) Motor responses to MC stimulation had latencies as much as 2 msec greater than those to electrical stimulation, suggesting that muscle responses were mediated by indirect (I) and direct (D) corticospinal discharges with MC and electrical stimuli, respectively (Day et al. 1987, 1989). However, by using

an appropriately tilted, lateral-sagittal orientation of a strongly energized MC, motor responses to MC and focal anodic stimulation during voluntary contraction could be equalized (Amassian et al. 1987a, 1989a). We proposed that the *orientation* of the round MC was a crucial determinant of whether the earliest corticospinal tract (CT) activation was a D or I discharge. A lateral-sagittal orientation led to an electric field more nearly paralleling the trajectory of CT neurons and therefore exciting them directly, while a vertex-tangential orientation led to an electric field whose lateral portions excited corticocortical afferent fibers and the previously described deep tangential fibers of the grey matter, leading to I discharge (Amassian et al. 1987b; Day et al. 1987; Rothwell et al. 1987). This hypothesis was seemingly supported by the finding in "killed end" recordings from the lateral CT of macaques that a lateral-sagittal orientation of the round MC elicited D discharge by CT neurons at lower intensities than I discharge, while the vertex-tangential orientation elicited I discharge at lower threshold than D in 2 of the 3 macaques tested. However, regardless of the orientation tested, if the intensity of MC stimulation

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was sufficiently increased, both D and I discharges were elicited (Amassian et al. 1990).

A radically different explanation for the latency difference between motor responses to MC and electrical stimulation was advanced by Edgley et al. (1990), who found in macaques that D responses to MC and electrical transcranial stimuli differed, electrical stimulation at increasing intensity leading to such marked reductions in latency that CT excitation appeared to have occurred close to the medullary pyramid. Recordings of the D discharge in humans also revealed a large reduction in latency at greatly suprathreshold intensities of electrical stimulation (Burke et al. 1990). Edgley et al. (1990) proposed that MC stimulation yielded a stable, longer D latency because the initial segment of the CT neuron was excited, while electrical stimulation could elicit a much shorter D latency because of excitation at great distance below the motor cortex. This hypothesis appeared to be supported by their claim that MC stimulation could not elicit I discharge (Edgley et al. 1989), or could only do so at higher intensities than were required for D discharge (Edgley et al. 1990); (but see the Discussion below for their most recent findings).

In attempting to decide between the different hypotheses of CT activation, excitation of a peripheral nerve model by the MC has certain advantages over the motor cortex, including: (1) the absence of synapses, (2) the orientation of the nerve fibers can be directly visualized, and (3) the basic mechanisms of excitation of peripheral nerve fibers are better understood. In the following account, the effects of changing the orientation and the shape of the MC are tested on mammalian phrenic and amphibian sciatic nerve preparations suspended in the appropriate Ringer's solution filling a brain-shaped container, the interior of the skull; in addition, the effect of a bend in the nerve trajectory is studied. A preliminary account of our findings was published elsewhere (Amassian et al. 1992).

Materials and methods

Amphibian nerves

Most of the earlier experiments were done with amphibian nerves. The sciatic nerves of 5 bullfrogs were dissected centrally to the vertebral column and the peripheral branches to the posterior tibial and peroneal nerves down to the ankle. The series also included two toads (*Bufo marinaris*). Immediately after dissection, the nerves were immersed in amphibian Ringer's solution and either mounted in the volume conductor for study or refrigerated until the next day; exceptionally, useful data were obtained 2 days after the nerve was removed from the animal.

Mammalian nerves

The mammalian phrenic nerve shares with the amphibian sciatic nerve preparation the advantage of length without the disadvantage of repeated branching. (Branching introduces the serious disadvantage that stimulation could occur at a cut branch rather than at some site along a population of fibers running the entire length of the preparation.) After observations for other experiments, the phrenic nerves of two cats and one macaque monkey were exposed under deep Na pentobarbital anesthesia, or immediately after death. The nerves were dissected from the diaphragm to the cervical roots and placed in mammalian Ringer's solution. They were used soon after removal.

Human subjects

Three of us served as subjects in a test of predictions derived from the nerve model.

The volume conductor

A plastic human skull was used to approximate the shape of the brain. To be able to visualize the nerve trajectory, the plastic portions representing hard palate and petrous temporal bones were excised. The skull was then inverted and fixed with a clamp on its far lateral side so the MC had an unobstructed contact with the skull. The positions of "C_z" and a point approximately 6 cm lateral to C_z in the interaural line were marked on the skull, the lateral point approximately corresponding to the region overlying the cortical representation of the hand. The inverted skull was filled with Ringer's solution of tonicity appropriate for amphibian or mammalian nerve. The temperature of the volume conductor was usually 22°C; although conduction velocity of the phrenic nerve would clearly have been higher if the nerve were at normal body temperature (e.g., 39°C), the lower temperature helped by magnifying the latency difference for a given change in site of stimulation.

MC and electrical stimulation

The MCs used were either the round epoxy-covered model (outer diameter 9.4 cm) or the figure 8 model (outer diameter 4.8 cm × 10 cm); both MCs were manufactured by Cadwell Laboratories, Kennewick, WA. The MCs were energized by a Cadwell MES-10 stimulator that was modified by external hardware (1) to deliver a pulse that was nearly unidirectional in amplitude and (2) to permit reversing the monophasic current in the MC windings without moving the MC (Maccabee et al. 1991). The electric fields induced by the round and figure 8 MCs in both restricted and large volume conductors have been experimentally recorded (Maccabee et al. 1990), but such recordings have not yet been made in the skull. However, computed electric fields for a *spherical* volume conductor

are available (Cohen and Cuffin 1991; Grandori and Ravazzani 1991).

To determine *where* along the nerve trajectory an MC elicited discharge originated, a bipolar electrode was later introduced into the volume conductor and tested along the course of the peripheral nerve. The electrode consisted of two Ag wires, each 325 μm in diameter, which were insulated with teflon except at the tips. A rectangular pulse, 100 μsec in duration and isolated from ground by a radio frequency unit, was used to stimulate the nerve. When the latencies of MC and electrically induced nerve responses approximated one another, the site of excitation by the MC was inferred to be at the site of electrical stimulation.

Peripheral nerve recording

Both ends of the nerve were ligated. At the recording end (defined here as the proximal end), the nerve emerged from the volume conductor posteriorly near the midline and was recorded monophasically in air with bipolar Ag electrodes. The nerve was coated with a petroleum jelly-mineral oil mixture to protect it from drying. The volume conductor was grounded at a point that empirically minimized the MC stimulus artefact.

The trajectory of the nerve varied with the purpose of the modelling and is identified in the appropriate section of Results. In general, the ligature at the distal end of the nerve was attached to the inner table of the plastic skull by the pressure of a small diameter, wooden end of a clamped Q-tip. The subsequent trajectory of the nerve was arranged as desired by gently looping around the nerve cotton threads that were attached above to the margins of the skull.

Nerve action potentials were conventionally resistance-capacity coupled amplified, with a bandwidth of 0.8 Hz–10 kHz and were displayed on a digital memory oscilloscope for photographic recording.

Human muscle recording

Recordings were made from abductor pollicis brevis (APB) and abductor digiti minimi (ADM) with disc electrodes (1 cm in diameter) attached to the skin over the muscle. Compound muscle action potentials (CMAPs) were conventionally amplified with a bandpass of 0.8 Hz–10 kHz and stored on a multichannel FM tape recorder with a bandpass of DC–2 kHz. The recordings were subsequently played back, computer averaged and displayed by an analog X-Y plotter.

Results

Modelling MC excitation of hand muscle-related CT neurons

To define positions relative to one another along the peripheral nerve, a "proximal" site refers to one closer

to the *recording* electrodes than a "distal" site. In the simplest model, the phrenic nerve trajectory initially approximates a tangent to the posterior portion of the round MC (Fig. 1, left and middle). The distal end of the nerve is at the "hand" region, the nerve then running for 31 mm upwards towards the base of the inverted skull before bending posteriorly towards the recording electrodes. Given that the MC is round, the initial straight portion of the trajectory cannot parallel the windings for any significant length. Nevertheless, the induced electric field does not cut across the initial segment of the nerve fibers at 90°. Thus, a component of current can flow longitudinally down the axoplasm and outward through the nerve membrane, a requirement for excitation (Rushton 1927). When the direction of current is clockwise in the MC (Fig. 1, left), the induced electric field is anticlockwise, i.e., the distal end of the nerve is positive relative to the first bend. With this arrangement, a large compound nerve action potential was elicited with typical monophasic configuration. Electrically stimulating the nerve at the bend yielded a compound action potential with latency similar to that elicited by an electric field orientated (− +) latero-medially. The time to peak of MC and electrically elicited responses were 1.05 and 1.23 msec, respectively. Thus, the MC excited the nerve fibers by causing current to flow outwards at or very near the bend.

Reversing the direction of current in the MC resulted in a significant increase in latency (1.2 msec) of
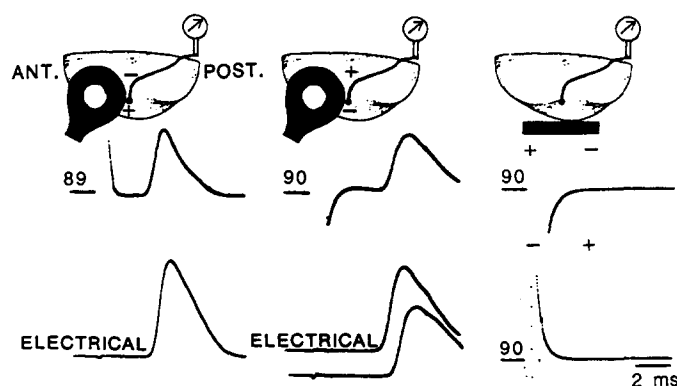

Fig. 1. Effect of changing the orientation and direction of current in the round MC on excitation of monkey phrenic nerve immersed in mammalian Ringer's solution in an inverted plastic skull. Top row, diagrams show a side view of the skull, the differing positions of the round MC and the direction of the induced electric field in relation to the nerve. Middle row, corresponding compound nerve action potentials recorded at the indicated MC stimulus intensities. Negativity of the recording electrode closest to the volume conductor is signalled by an upward deflection. Bottom row, responses to electrical stimulation at the bend (left) and at two locations closer to the (distal) end of the nerve at the skull; right, no response to a vertex-tangentially orientated MC even when the current is reversed. The latero-medial orientation is directed downwards in the inverted skull, but upwards in the erect human.
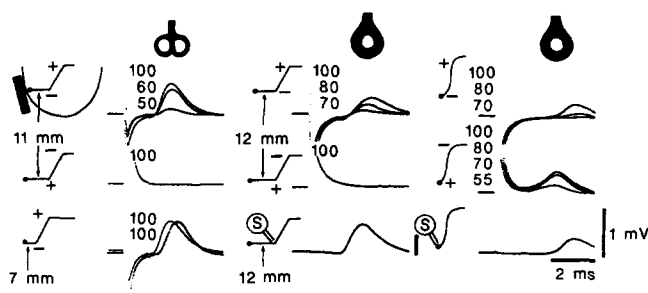
Fig. 2. Influence of a bend in cat phrenic nerve and effect of changing the direction of current on excitation by figure 8 and round MCs. Top, the type of MC utilized for each recording below. First column left, the side view of the inverted skull in Fig. 1 is now replaced by a coronal section of the skull showing the initial radial trajectory of the nerve followed by an (anatomical) ventro-posterior trajectory towards the (inverted) base of skull. The junction region of the figure 8 MC overlies the distal nerve end. The distance from the nerve end (at the skull) to distal (first) bend is 11 mm for top and middle recordings and 7 mm for bottom recording. Second column from left, top recording shows responses at the indicated stimulus intensities when induced electric field polarity leads to negativity at the distal bend; middle, no response at 100% intensity when polarity reversed; bottom recording shows superimposed responses when distal bend is 11 and 7 mm, respectively, from distal end of nerve. Third column from left, top and middle recordings show comparable observations when posterior windings of round MC over end of nerve; bottom, nerve response has same latency when distal bend electrically stimulated. Right column, effect of removing the initial radial trajectory; top recording, induced negativity at nerve end excites there and is matched by electrical stimulation near end of nerve (bottom).

the compound nerve action potential and its temporal dispersion was also increased (Fig. 1, middle). Clearly, when the electric field was directed (+ −) latero-medially, the MC excited the nerve distal to the bend, i.e., near the skull inner table. Electrical stimulation approximately 15 and 10 mm from the distal end elicited responses with latencies straddling that of the response to MC stimulation. Typically, conduction velocity was reduced near the killed end of the nerve; presumably, the partially depolarized nerve membrane partially inactivates voltage-gated sodium channels, thereby reducing action potential propagation velocity. In some instances, stimulation with the electrodes at the distal end of the nerve failed to elicit a nerve response with as long a latency as that elicited by the MC. Apparently, stimulation by the electrical pulse spread to less damaged regions proximal to the nerve end.

When the round MC was orientated vertex-tangentially (Fig. 1, right), no responses by the nerve were elicited with either polarity of the electric field. In other experiments where the nerve threshold was lower, responses were elicited with the vertex-tangential orientation, but at markedly elevated threshold (Fig. 1 in Amassian et al. 1992).

The above model has an anatomical shortcoming in lacking a significant radial component of the initial trajectory, i.e., perpendicular to the equivalent of the

cortical surface. In Fig. 2 (second column from left), the distal end of the nerve is given an initial 11 mm radial trajectory. The long axis of the junction region of a figure 8 MC was orientated latero-medially. A (+ −) latero-medial orientation of the induced electric field excited the cat phrenic nerve at low threshold, but the reverse orientation (below) failed to excite the nerve even at 100% stimulator output. Reducing the length of the radial trajectory from 11 to 7 mm caused an increased latency of the nerve response to the (+ −) orientation, i.e., excitation occurred more distally (bottom record). Qualitatively similar results were obtained when the posterior portion of a round MC replaced the junction region of the figure 8 MC (third column from left). Electrical stimulation at the first bend, i.e., where the nerve moves from the radial trajectory toward the base of the skull, elicited nerve responses of comparable latency to those elicited by the MC induced (+ −) electric field (bottom record). The time to peak of MC and electrically elicited responses were 1.1 and 1.0 msec respectively. When the initial radial component of the trajectory was lacking (rightmost column), the (+ −) latero-medial orientation of the MC induced electric field then excited the nerve at its distal end (cf., the response to electrical stimulation, bottom record). The (− +) orientation of the electric field successfully excited the nerve more proximally.

Modelling MC excitation of foot muscle-related CT neurons

Foot muscles are represented on the medial aspect of the hemisphere in the paracentral lobule (Penfield and Boldrey 1937). Therefore, a cat phrenic nerve was given an initial medio-lateral trajectory, i.e., equivalent to a radial trajectory with respect to the buried medial surface of the cortex (Fig. 3, left). Subsequently, the trajectory was directed posteriorly and upwards towards the base of the inverted skull. The long axis of the figure 8 MC junction was transversely orientated to the skull and therefore parallel to the initial radial, nerve trajectory. The lowest threshold excitation occurred when the MC induced an electric field orientated (+ −) medio-laterally (middle column). Electrical stimulation at the first bend elicited a nerve response with a similar latency (bottom record). Reversing the electric field induced by the MC also excited the nerve, but at higher threshold and with an increased latency (right column). As indicated above, electrical stimulation at the nerve end elicited a response at slightly shorter latency than with MC stimulation, presumably because of spread proximally to a less damaged region.

In other recordings, the tangentially orientated round MC also readily excited nerve in the "leg" model provided that the anterior or posterior windings overlay the initial *radially* directed portion of the nerve.
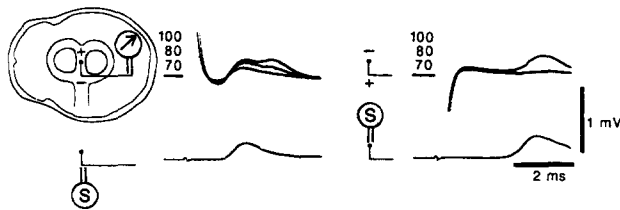
Fig. 3. Effect of changing the direction of current in the figure 8 MC on excitation of cat phrenic nerve, modelling leg CT neurons. Top left, diagram of the inverted skull now viewed from above. Figure 8 MC tangential to the vault. The nerve was given initially a lateral trajectory (corresponding to a radial trajectory from the paracentral lobule on the medial aspect of the hemisphere). Middle and right columns top, nerve responses at the indicated intensities and polarities of MC stimulation; bottom, nerve responses to electrical stimulation at the indicated positions.

With this orientation, the transversely directed portion of the electric field approximately parallels the initial radial trajectory of the nerve.

Modelling MC excitation of corticocortical fibers

In the monkey, electrical stimulation of premotor and postcentral cortex powerfully activates CT neurons indirectly (Patton and Amassian 1954, 1960). However, the major motor information flow in humans is believed to be from supplementary motor cortex and area 6 towards area 4 posteriorly (e.g., Roland et al. 1980). Therefore, the initial attempt at modelling corticocortical excitation with a vertex-tangentially orientated MC utilized a nerve trajectory that originated anteriorly, subsequently running posteriorly to about the midpoint of the lateral portion of the MC when the nerve trajectory was directed upwards towards the inverted base of the skull (Fig. 4, top row). Symmetry was attained by having the most distal portion of the nerve similarly bent upwards. Although, corticocortical fibers in the brain clearly bend in the opposite direction, i.e., towards the vault rather than the base of the skull, the electrical consequences of the bend are qualitatively unchanged by the direction of the bend, as indicated in Discussion. Because the recording was made from the bullfrog sciatic nerve preparation, in order to detect any asymmetry, the nerve was recorded successively from the peripheral and then from the central ends. The antero-posterior trajectory of the corticocortical fiber model was 35 mm. Regardless of which end was recorded, responses were obtained when the lateral component of the induced electric field was orientated (+ −) in the antero-posterior axis (Fig. 4). When the field was reversed, no responses were elicited even at 100% stimulator output. The latencies of the MC-elicited nerve responses were matched (left and right columns) by electrical stimulation 4 and 6 mm, respectively, in front of the posterior bend of the nerve (left, bottom). The time to peak was 0.48 msec with both types of stimulation.
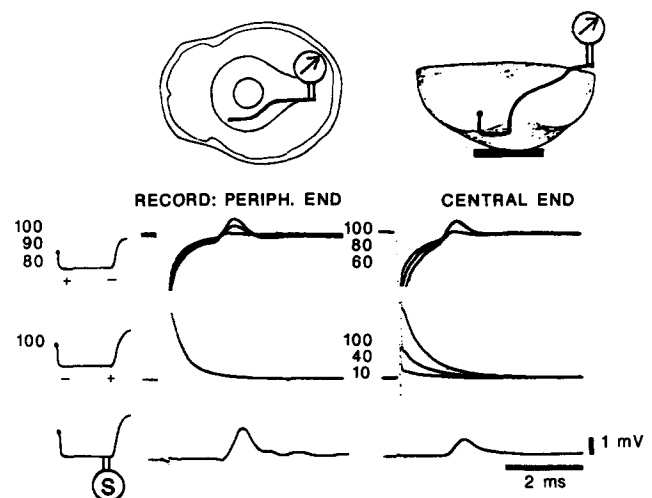

Fig. 4. Effect of changing the direction of current in the round MC on excitation of the bullfrog sciatic nerve preparation, modelling anterior corticocortical fibers. Top, diagrams showing the inverted skull viewed from above (left) and laterally (right). Round MC tangential to and centered near vertex. Second row, across from left, shows polarity of field and MC stimulus intensities, responses at these stimulus intensities when recording from peripheral and central ends, respectively, of the nerve. Third row, effect of reversing the polarity of the induced electric field. Bottom row, electrically induced nerve responses when stimulated 4 mm (left) and 6 mm (right) distal to bend. Length of nerve at the vault 35 mm.

To model corticocortical fibers ending in precentral gyrus and originating in the adjacent postcentral gyrus, a postero-anterior trajectory of 2 cm was chosen (Fig. 5). Although the difference in threshold is not as marked as in Fig. 4, the (+ −) induced electric field in the postero-anterior axis elicited a nerve response at lower threshold and with a longer latency than the reverse field. Electrical stimulation (bottom records) disclosed that the longer latency, MC-elicited response
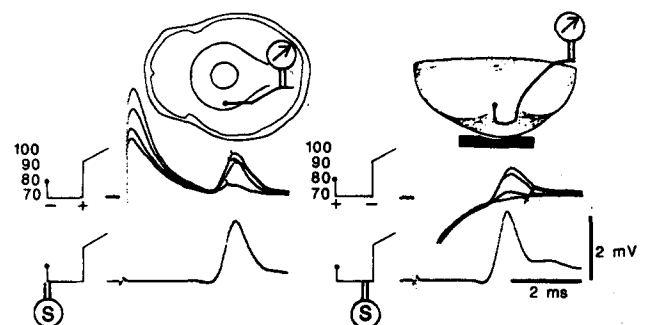

Fig. 5. Effect of changing the direction of current in the round MC on excitation of the bullfrog sciatic nerve preparation, modelling posterior corticocortical fibers. Recording from peripheral end. Top, diagrams showing skull viewed from above (left) and lateral aspect (right). Round MC tangential to and centered near vertex. Second row, across from left, shows polarity of field and MC stimulus intensities, nerve responses at these intensities and effect of reversing the polarity of the induced electric field. Bottom, responses to electrical stimulation of the nerve near distal (left) and proximal (right) bends.
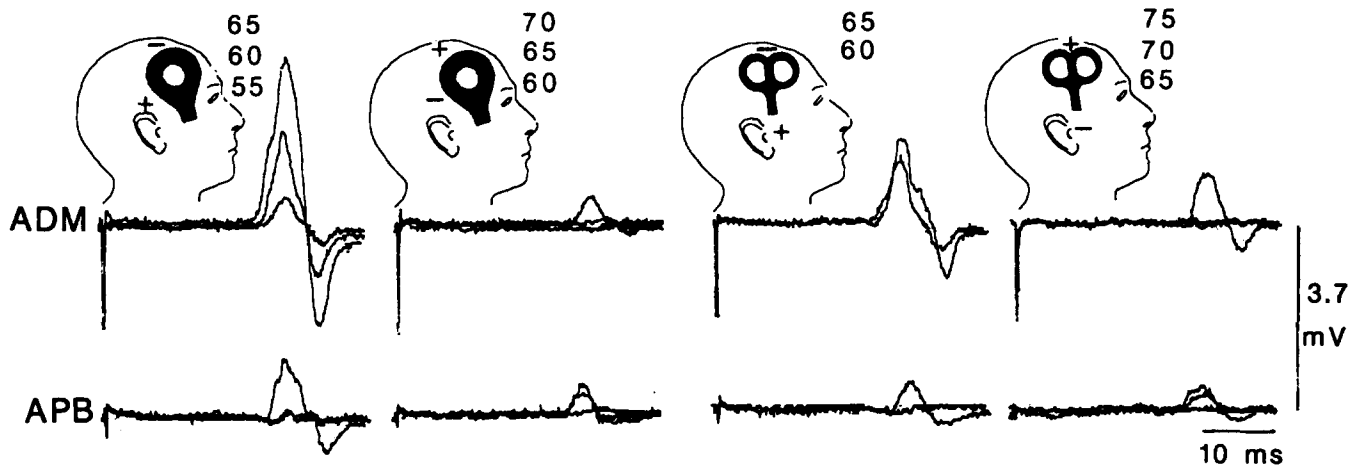
Fig. 6. Effect on responses of contralateral ADM and APB of changing the direction of current in laterally sited, round and figure 8 MCs. Four responses summed at each of the indicated MC stimulus intensities and polarities of the induced electric field.

originated close to the anterior bend (corresponding to precentral gyrus) and the short latency response arose just anterior to the posterior bend. The time to peak of MC and electrically elicited responses was 0.64 and 0.59 msec, respectively.

Influence in humans of direction of current in the MC

Barker et al. (1987) observed that a vertex-tangentially orientated MC, when energized by a pulse that was substantially unidirectional, preferentially activated limb muscles on one side of the body. This observation has been repeatedly confirmed by others; the *corrected* direction of the induced field that preferentially activates motor cortex is (+ −) in the postero-anterior axis (reviewed in Rothwell et al. 1991). We confirmed that a vertex-tangential orientation of the round MC preferentially activates the arm representation in motor cortex when the electric field has the above orientation. Utilizing double coil stimulation with the junction region orientated transversely across the midline, the most recent findings of Cracco et al. (1991) show that leg muscle responses have the lowest threshold when the induced electric field is orientated (+ −) in the medio-lateral axis.

Although we have repeatedly tested a polyphasic pulse in the past, the effect of changing the direction of monophasic current in a round MC orientated lateral-sagittally has not previously been tested. An opportunity was therefore provided to test a prediction from the model. Thus, Fig. 2 implies that an induced electric field orientated (+ −) latero-medially should excite the hand muscle-related CT neurons at lower threshold than the reverse orientation. In Fig. 6, the posterior part of a round MC (left two columns) and the junction portion of a figure 8 MC (right two columns) were near optimally positioned for ADM. As predicted by the model, the lowest threshold ADM responses in

a relaxed subject were obtained with the (+ −) orientation. In another subject, at 80% stimulator output the (+ −) latero-medial polarity yielded a clear flexion of the digits during voluntary contraction, but nil when the current was reversed. Minimal motor responses commenced at 90% reversed output. Thus, the model predicted correctly the optimal orientation of the field.

Discussion

Limitations of the peripheral nerve-skull model

Ideally, a continuous set of nerve fibers with a range of diameters comparable to that of the CT would be available for testing in a brain-shaped volume conductor with anisotropy at the appropriate sites (e.g., Ranck and BeMent 1965). At least at the fast fiber end of the spectrum, the mammalian phrenic nerve approaches this requirement, but the fiber bundles are invested in connective tissue sheaths; any local breaching of the epi- or perineurium during dissection would create a low resistance pathway for current and effect the site of excitation by the MC. Although readily available, the amphibian sciatic nerve and its branches pose special problems when recorded either peripherally or centrally. Recording from a branch peripherally has the advantage that a given set of nerve fibers running the full length of the nerve is tested. However, the resistance to flow of stimulating currents presented by other nerve fibers is clearly reduced distal to each branch. Recorded centrally, MC excitation of a cut branch must be excluded, but the fibers at the peripheral end near the skull are not contaminated by unrecorded fibers and are therefore most exposed to the electric field. Recording from the peripheral end is probably preferable, but our results with recording at

either end were qualitatively similar to one another and to those obtained from mammalian phrenic nerve.

It was assumed that the fastest fiber responses to MC and electrical stimulation were, if not identical, at least drawn from the same subpopulation. A major source of error in localizing the site of MC excitation would result if the MC excited only significantly slower fibers. The similarity of the time-to-peak of the compound action potentials suggests that a similar population of fast nerve fibers was excited by MC and electrical stimuli. However, the *trailing* edge of the compound response occasionally differed (e.g., Fig. 3, left), suggesting that the MC can excite (phrenic) nerve at several sites.

Theoretically, if hyperpolarization of nerve *proximal* to the site of excitation were sufficient to slow conduction velocity, then the excitation site might be erroneously attributed to a more distal point. However, in an intensity series, any such effect would be manifested by an increased latency of response with strong stimulation, which was not observed.

A comparison of direct excitation in the peripheral nerve-brain-shaped volume conductor and an in-vivo model, the monkey brain, is of interest. The monkey brain has the advantage that primate CT neurons with associated anisotropies of the volume conductor are studied; furthermore, the conditioning effects on direct excitation of ongoing synaptic bombardment can be used to identify the initial segment as one site of electrical (focal cathodal) and MC excitation of the CT neuron (Amassian et al. 1990). However, localizing the site of excitation by the MC with electrical stimulation along the nerve is much easier in the peripheral nerve model. Furthermore, the similarity in dimensions between the contents of the plastic skull and the human brain avoids the mismatch between MCs designed for human transcranial stimulation and the monkey brain. The mismatch is especially grave when using the Novametrics Inc. MC (outer diameter 14 cm); when centered on the vertex, the lateral portions of this MC would lie far lateral to the arm area of the macaque brain (Amassian et al. 1990).

The influence of a nerve bend on excitation

Classical axonology relates transmembrane current in a nerve fiber to the second derivative of the external voltage in the long axis of the fiber (Katz 1939; Rattay 1986; Reilly 1989). The implications of this relationship include: (1) a nerve fiber in a uniform electric field has no transmembrane current and therefore cannot be excited; (2) a finite second derivative can be achieved when the nerve fiber parallels a non-uniform electric field, as in Fig. 7A (Durand et al. 1989; Roth and Basser 1990) or when it bends in either direction away from a uniform field (B), or the uniform zone of an electric field curves away from a straight nerve fiber
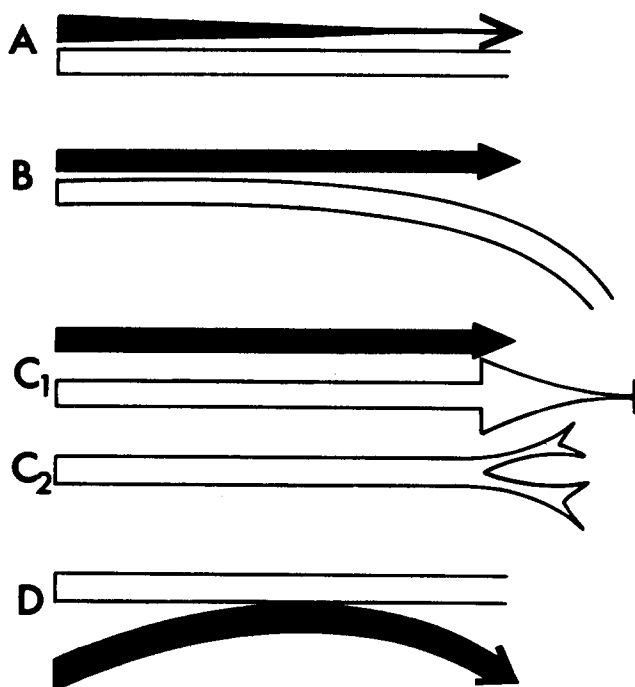

Fig. 7. Diagram of some of the possible relationships between an applied electric field and a neuron (especially its axon), which can lead to excitation. C_1 is not favorable for corticospinal neuronal excitation because of the inexcitability of the apical dendrite (cf., the initial segment, Amassian et al. 1990). C_2 is also unfavorable for excitation because of the low excitability of fine preterminal branches where the core resistance is high.

(D). A nerve fiber *terminating* in a uniform electric field (C_1 and C_2) is a special case where transmembrane current can also flow (Reilly 1989), but is believed to be less important than other factors in the cortex (see below). In all cases, membrane current must be outward for excitation to occur. A preliminary analysis of nerve excitation in a rectangular trough by a figure 8 MC disclosed that excitation occurred under whichever end of the junction a negative-going spatial derivative of the electric field was maximal (Maccabee et al. 1992).

The major influence of a bend in determining the site of MC excitation of nerve was manifest through most of this study. In each case, the polarity of the electric field that was effective led to outward current there. This finding is unlikely to reflect an error due to cut nerve branches because it was obtained with mammalian phrenic nerve. Furthermore, altering the site of the bend causes an appropriate change in site of excitation, implying that the bend was the important factor. Admittedly, the angle at the nerve bend in the model is most likely more acute than the curvature of CT axons in white matter. However, such curvature is likely to be most pronounced superficially where sulci tend to undercut the grey matter, causing "funneling" of CT fibers before entering the radiations. The elec-

tric field induced by the figure 8 MC would be powerful at such superficial levels, but rapidly attenuates in intensity (in a homogeneous volume conductor) between depths of 2 and 3 cm (Maccabee et al. 1990). The electric field induced by the tangentially orientated *round* MC at depth does not attenuate so rapidly (Barker et al. 1987; Maccabee et al. 1990), thus permitting stimulation of curved portions of the CT fiber trajectory deeper in white matter.

Where a round or a figure 8 MC is tangentially applied to the boundary of a finite volume conductor, there is general agreement that the major induced currents near a curved or boundary flow parallel to it (Tofts 1990; Cohen and Cuffin 1991). This implies that the *initial*, radially directed fibers of CT neurons located on the crown of a gyrus will not be directly stimulated because the electric field is orthogonal to them. CT neurons situated in the anterior bank of the precentral gyrus would appear to be exceptions, but even there the CT fiber trajectory has a major component directed medio-ventrally rather than in the antero-posterior axis. However, the localization of the point of stimulation by double coil MCs to the deeper layers of grey matter (Epstein et al. 1990) is probably too superficial for *direct* excitation of CT neurons located on the crown. Assuming their calculations of the depth are correct, it appears more likely that in their experiments CT neurons were *indirectly* activated through their tangentially orientated synaptic inputs. (This surmise could have been tested by determining whether the CMAP latencies differed with focal anodic and double coil stimulation.) It must be emphasized that anatomical terms such as "radial" and "tangential" strictly relate to the cortical surface, however infolded; they bear no relationship to the *geometric* radius of, or *tangent* to a *sphere*. Thus, the trajectory of CT fibers originating in the crown rapidly ceases to be radial in the geometric sense and more nearly parallels the anterior or posterior portions of the electric field induced by, e.g., a round MC, which has a tilted lateral-sagittal orientation (Fig. 1 in Amassian et al. 1990). The difference between anatomical and geometric definitions can lead to confusion in theoretical modelling.

Although the nerve model implies that the influence of a bend is greater than "end" excitation near the inner table of the plastic skull, it does not follow that the same would apply to CT neurons in human brain. The damaged, ligated end of a nerve is not equivalent to healthy neural membrane. However, the "end" portion of the CT neuron directed towards the pial surface is considered to be electrically inexcitable (Amassian et al. 1987b); thus, current exit at the "end" portion would be expected to be ineffective for direct excitation of the CT neuron. These inferences required experimental testing in humans. The prediction was verified that an induced electric field with a polarity

causing outward current at the bend (rather than at the "end"), yielded hand muscle responses at lower threshold (Fig. 6).

The influence of MC orientation on excitation

The importance of the orientation of the MC relative to that of cortical neurons in determining their direct excitation (Amassian et al. 1990) is clearly evidenced in the skull-peripheral nerve model. When the nerve is positioned approximately where *hand-related* CT would originate, a vertex-tangentially centered round MC is relatively ineffective in directly exciting the nerve. However, when the MC is moved anteriorly or posteriorly so that the windings overlie the putative initial trajectory of *foot muscle-related* CT neurons, the nerve is readily excited directly. This finding emphasizes the difference in direct excitation of hand and foot-related CT neurons in the human (Iles and Cummings 1992) and is paralleled by the finding in humans of a similar optimal orientation of the round MC for foot responses (Rosler et al. 1989; Cracco et al. 1991). By contrast, in our skull model, peripheral nerve positioned in relation to hand area of motor cortex is directly activated when the MC is moved to a tilted, lateral-sagittal location; this is precisely the orientation required for equal latencies of forearm arm and hand muscle responses to focal anodic and MC stimulation during voluntary contraction (Amassian et al. 1987a, 1990).

The final type of modelling relates to direct activation of corticocortical fibers, which indirectly activate CT neurons. Regardless of whether the peripheral nerve trajectory ran posteriorly or anteriorly towards the interaural line, the vertex-tangentially orientated round MC excited the peripheral nerve model. With both anterior and posterior trajectories, optimum stimulation occurred with negativity of the induced electric field near the interaural line; this result seems surprising given that each nerve model for corticocortical fibers has both an anterior and a posterior bend. However, for each of the two corticocortical trajectories, the bend closer to the interaural line is located where the electric field intensity is maximal and is orientated nearly parallel to the nerve fibers. In humans, the electric field polarity induced by the vertex-tangentially orientated MC that optimally elicits limb responses is generally agreed (see Results) to be $(+ -)$ in the *postero-anterior* axis. Thus, the nerve model leads to the unexpected conclusion that excitation of corticocortical fibers from parietal lobe rather than premotor cortex is responsible for the lowest threshold limb responses.

A detailed comparison of the influence of orientation and bends of nerve fibers in the skull model on the direct CT responses to MC and electrical transcranial stimuli in the human requires knowing the trajectories
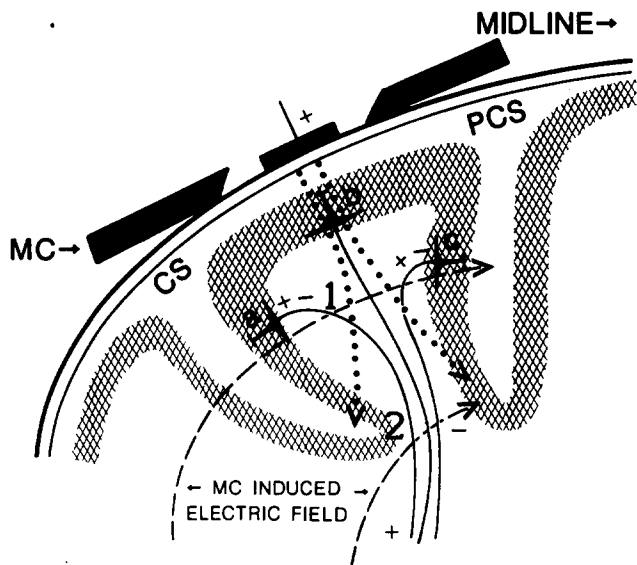
Fig. 8. Diagram of the relationship of the electric fields induced by a focal anode and an MC to precentral corticospinal neurons and their fiber trajectories in coronal section. CS, central sulcus; PCS, precentral sulcus. Either the junction region of the figure 8 or anterior or posterior windings of the round MC are orientated laterally over arm area as in Fig. 6. The electrically applied field is indicated by a dotted line. MC induced fields at two depths with their polarities indicated by interrupted lines. b, a and c are CT neurons in the crown and in cortex buried in sulci, respectively.

of the CT neurons. (The electrical transcranial stimuli referred to are delivered between a small anode over arm area and a much larger, distant cathode, Amassian et al. 1989a.) The deep infolding of the precentral gyrus at the central and precentral sulci and its tortuosity along the lateral-medial axis implying that many CT neurons have a complex trajectory. For some, the initial trajectories curve towards one another (1 in Fig. 8), before curving deeper into the radiations, e.g., from the anterior and posterior banks of the central and precentral sulci, respectively. Subsequently, both sets of CT fibers join those from the crown of the precentral gyrus in a major curve (2 in Fig. 8) directed medio-ventrally and posteriorly. The "undercutting" of the precentral gyrus by the central and precentral sulci contributes to the acuteness of curve 2. Clearly, these are not the only possible curves in the CT trajectory, but are intended to convey the dominant, overall vectors of the fiber trajectories near motor cortex.

A round MC applied laterally over arm motor cortex induces an electric field under either the posterior or the anterior windings approximately parallel to the CT neuronal trajectories before curve 1; if the polarity of the field results in outward current at this bend for CT neurons (a) originating in the anterior bank of the central sulcus, then by contrast, current would flow inward at the corresponding bend in CT neurons (b). Regardless of polarity, the current would be nearly perpendicular to CT neurons (c) originating in the

crown. (Coronal sections through the cerebrum show the precentral gyrus cut on a slant rather than displaying the anterior bank parallel to the coronal plane.)

Even before the first bend, CT neurons have tangentially directed axon collaterals in lamina V, which give rise to occasional late D responses of PT neurons with electrical stimulation (Rosenthal et al. 1967). However, it seems unlikely that these thin fibers would be excited by the MC pulse, considering the difficulty of exciting all the alpha motor axons in a peripheral nerve (Amassian et al. 1989b).

At the next major bend (2), the induced electric field would result in outward current in the fiber trajectories of CT neurons (a, b and c). Focal anodic stimulation would lead to outward membrane current in white matter; given a point source, the inverse square relation between current density and depth implies that even the relatively straight trajectory of CT neurons (b) would be compatible with excitation. However, the large area of a focal electrode (1–5 cm^2) and the high resistance of the skull tend to increase the area of pia traversed by the current thus, for CT neurons in the center of the electric field, the inverse square relation would not hold and any fiber curvature would be important. In the monkey, focal anodic excitation of CT neurons in the gyral crown occurred distant to the synaptic inputs, i.e., at least 2 nodes distal to the initial segment, placing the site of excitation in white matter (Amassian et al. 1990). Although the electric field vectors induced by the MC pulse and focal anode are nearly orthogonal to one another, membrane currents would flow outwards from CT fibers at curve 2 in close proximity to one another. The identity of muscle response latencies with focal anodic and lateral-sagittal MC stimulation is consistent with this hypothesis. In the human, a more rigorous test is provided by the near-threshold summation of focal anodic and MC transcranial stimuli, which has a time constant (approximately 100 μsec) similar to that measured in ulnar motor axons (Rothwell et al. 1992); this implies that the electric fields from near-threshold focal anodic and the laterally sited MC stimuli excite nodal membrane of overlapping populations of CT fibers, rather than the MC exciting neural membrane with a longer time constant, such as the initial segment (cf., Edgley et al. 1990).

Why do latencies of motor responses to electrical and vertex-tangential MC stimulation differ?

The conclusions from the peripheral nerve-skull modelling unequivocally imply that the increased latency of arm muscle activation by the vertex-tangentially orientated round MC results from synaptic delays in activation of CT neurons, e.g., through corticocortical fibers, and possibly the deep tangential plexus in gray matter described in Amassian et al. (1987b). Ex- ·

cept at intensities greatly suprathreshold for movement, CT neurons supplying hand muscles would not be directly activated by such MC orientation. By contrast, the model implies that the round MC tangential to, but not centered at the vertex, could directly excite CT neurons related to foot muscles; as a corollary, no difference would be expected in latency of response of foot muscles to electrical and MC stimulation. Significantly, Iles and Cummings (1992) failed to record any latency difference in leg muscle responses to these two types of stimulation.

The alternative explanation for the latency difference in arm muscle responses envisages both that the vertex-tangentially orientated MC directly activates arm-related CT neurons at the initial segment and that electrical stimulation activates CT fibers at a great distance below motor cortex, e.g., as low as the medullary pyramid (Edgley et al. 1990). A major support for this theory, the supposed inability of the MC to elicit indirect CT discharge in the monkey (Edgley et al. 1990) has been lessened by their most recent finding that at least 40% of individual CT fibers had a *lower* threshold to indirect than direct activation (Edgley et al. 1992). Because the CT fibers were recorded by them at low thoracic levels, they were probably mostly related to leg muscles, i.e., where a latency difference would not even be expected in the human (Iles and Cummings 1992). Burke et al. (1990) confirmed in the human that the latency of the direct CT response could be substantially reduced by greatly increasing the intensity of electrical transcranial stimulation. However, the marked change in latency of the direct CT response occurred when the stimulus intensity was *above maximum* for the direct discharge (their Fig. 2). Their findings cannot account for the latency difference observed with submaximal electrical and MC stimuli and thus do not support the theory that electrical spread to the human brain-stem accounts for the latency difference between electrical and vertex-tangential MC stimulation.

Direct CT activation of arm-related neurons is predicted by the model when the MC is in a tilted lateral-sagittal orientation. In this orientation, human forearm and hand muscle responses during voluntary contraction have equal latencies to focal anodic and MC stimulation (Amassian et al. 1987a, 1989a). Furthermore, an orthogonal MC orientation over the arm motor area in the monkey elicits direct discharge by CT neurons at much lower threshold than indirect discharge (Amassian et al. 1990). These findings clearly differ from those obtained with the vertex-tangential orientation; thus, the weight of evidence favors the earlier explanation, based on direct versus indirect CT activation, for the different motor response delays in the human with anodic and vertex-tangential MC stimulation.

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