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Transcranial Magnetic Stimulation

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Abstract-**Transcranial Magnetic Stimulation (TMS), by providing a method of stimulating human brain without the need for surgical exposure or significant discomfort, facilitated the study of cerebral functions in both normal subjects and patients. The aspects of TMS treated include: (1) The part(s) of neurons readily direct excited by TMS; (2) the optimal relationship between the orientations of the electric field induced by TMS and the directly excited neurons; (3) the transynaptic effects of the directly excited neurons that are either distant or local; (4) the effects of repetitive versus single pulse TMS.**

I. Introduction

Electrophysiological exploration of the human brain was restricted during the late XIX and early XX Centuries to patients with cerebral cortex surgically exposed. The extent to which the remaining properties of such brains may have been altered by disease could not be reliably investigated. Remarkably, Penfield and Roberts [1] removed frontal lobe areas that included the speech expressive region (Broca's Area), in two patients with seizures and both were speaking within 24 hrs. The first major advance occurred when Merton and Morton [2] found that a high voltage electrical pulse applied to the head could penetrate sufficiently the high skull resistance to excite the motor cortex. This made possible experiments on normal subjects, in addition to patients. Specifically, central motor conduction time could now be measured. However, such electrical stimulation of motor cortex, although safe, was quite painful, feeling like a blow to the head. The introduction in 1985 of transcranial magnetic stimulation (TMS) by Barker and Associates [3] caused little discomfort to normal subjects and patients, thereby greatly enhancing its applicability in investigation. When first introduced, a brief, large current pulse was sent through a round coil of wire (o.d. 12.5 cm) centered on the head, generating a magnetic flux that readily penetrated the skull. The magnetic flux induced a current in the brain volume conductor in the reverse direction to that in the coils. The current intensity was maximal under the windings, i.e. stimulation of neurons theoretically could occur anywhere under the windings. Restricting the site of stimulation was first attempted by applying only the edge of the round coil to the head, requiring a tilt so that sufficient magnetic flux entered the brain. Such localized stimulation elicits preferential movements of individual digits and localized projected sensations [4,5]. An important technical advance was introduced by joining 2 round coils in a figure 8 such that the currents flowed in the same direction only in the junction region of the two coils. The induced electric field under the junction region is approximately 2x that elsewhere under the coils. Especially when stimuli a little above threshold are used, displacement of a figure 8 coil by as little as 0.5 cm, or a slight change in tilt if the coil is flat on the rounded head, can markedly change the physiological response. Such spatial resolving power should be distinguished from identification of the actual site of excitation (see below).

The use of TMS to excite neurons raises a number of questions, including: (1) What part(s) of neurons are directly excited at threshold intensity? (2) What is the optimal relationship between the orientations of the induced electric field and the directly excited neurons? (3) What are the transynaptic effects of the directly excited neurons?

1. The part of the neuron directly excited by TMS at lowest threshold

The brief TMS induced electric field excites electrogenic neural membrane when the membrane capacity, in parallel with the channel conductance, has been discharged to firing level of the action potential. The threshold is reached when the passively driven outward membrane current by the induced electric field is equaled by the inward current in the increasing number of open Na channels. On the basis of a simple RC model, Barker et al., [6] indirectly estimated that the membrane time constant of the neuronal part stimulated by TMS over motor cortex was ˜150μs, and similar to that of peripheral alpha motor axon. Rothwell et al., [7] estimated the membrane time constant more directly from the exponential time course of decay of facilitation of a motor response when a conditioning anodic electrical pulse was followed by a TMS test pulse oriented to induce a latero-medial (L-M) directed field. Both pulses were near threshold in intensity and were appropriately applied to excite directly (D) corticospinal tract (CT) axons. The time constant of decay was ˜100μs, equaling that of peripheral alpha motor axons and approximating the more reliable measurements on animal myelinated axons. Summarizing, the brief induced electric field induced by single pulse TMS machines is appropriate for exciting myelinated axonal membrane rather than membrane at the cell body with a much longer time constant.

Because action potentials at nodes of myelinated axons require minimal expenditure of energy compared with grey matter, metabolic indices of increased neural activity such as fMRI or PET do not reveal the actual site of TMS direct excitation. Rather, the more distant sites of afferent transynaptic, or antidromic excitation of cell bodies are revealed.

2. The relationship between orientations of the induced electric field and the myelinated axon trajectory.

Rushton [8] found that the efficacy of an electrical stimulus to a linear bundle of axons was proportional to the cosine of the incident angle of the current. Thus, at 90º penetrating a restricted area of nerve membrane and exiting the membrane a few μm away would usually fail to excite a sufficient area of membrane to set up a propagated impulse. Similarly, when the plane of a round coil whose edge touches skin over a nerve trunk is parallel to the nerve trajectory, excitation of the motor axons is maximal but is minimal if the coil is rotated through 90º. Thus, applying the cosine relationship to TMS of brain implies knowledge not only of the induced electric field orientation, but also the trajectory of the myelinated axons to be stimulated. For example, excellent motor responses were initially elicited by centering a large coil on top of the head. However, the TMS elicited responses were 1-2 ms later than those elicited by an anodic electrical pulse, which directly excited the CT fibers; at first, the difference in latency suggested a fundamental difference between electrical and TMS excitation of brain. Subsequently, by reorienting the TMS induced electric field by moving the coil to the side of the head, the latency difference between electrical stimulation and TMS disappeared, i.e. CT axons were directly stimulated by both types of stimulation [4].

Given the appropriate alignment of the induced electric field and the linear bundle of axons to be excited, what site along the axons would first be excited? The classical cable equations dating from a century ago predicted that the maximum changes in membrane potential, i.e. increase or decrease occurred at the spatial derivatives of an externally applied electric field. (In a uniform electric field, current exiting at a node would be equaled by current entering, i.e. there would be no net transmembrane current and therefore no excitation). Magnetic coil excitation differs from an externally applied current source in that the electric field is induced both outside and inside the axon. Where the induced electric field is uniform, no excitation can occur, but where it curves away from the linear axons, a negative spatial derivative is created and excitation occurs [9]. However, a cerebral cortical axon typically does not have a linear trajectory from parent cell body to synaptic ending on the cells it is connected to. In a model system consisting of peripheral nerve immersed in physiological saline contained in a plastic human skull, bends were made in the nerve to resemble those of CT fibers traveling from motor cortex towards the internal capsule. TMS applied to the skull in the L-M orientation excited the nerve fibers at such bends [10]. Similarly, if a straight peripheral nerve in a trough of saline is increasingly bent, the response to a given TMS excitation is progressively increased to 90º. Evidently, current driven inside the fiber, by the electric field can after fiber bending emerge where the electric field is lessened. Significantly, the maximum intensity of excitation was achieved not at the negative spatial derivative, but at the peak electric field intensity, i.e. corresponding to the midpoint of the junction of a figure 8 coil [9].

The clear difference in exciting function by a TMS induced field acting on linearly trajecting axons versus acting at a bend provides a possible method of identifying the site of excitation. For example, with the lower edge of a round coil or the junction region of a figure 8 coil symmetrically located over the lower occiput, a flashed word or three letters are best suppressed if viewed at the fovea, which is represented in midline calcarine cortex. However, the spatial derivatives are located maximally many cm lateral to the midline. The much greater efficacy of the field intensity versus its spatial derivative implies excitation at bends in axons, most likely geniculocalcarine, where they bend up or down into calcarine cortex [11]. The greater efficacy of the L-M compared with M-L orientation would fit induced intra-axonal current exiting medially at these bends. Similarly, optimal early transynaptic CT fiber and hand muscle excitation is secured when the peak field intensity (but not its derivative) is over motor cortex. Most likely current is induced in corticocortical axons from parietal lobe when the induced field is posterior-anterior (P-A) and exits the axons where they bend up from white matter into motor cortex. Again, the negative spatial derivative would be many cm distant from motor cortex.

The underlying assumption above is that optimal excitation by TMS requires knowing the trajectory of the axons to be excited; what if their trajectory is unknown? The possibilities are: (a) to make observations with a figure 8 coil systematically angulated around the clock face, i.e. obviously requiring many stimuli; (b) to test TMS with a small round coil (e.g. 5 or 6 cm o.d.), i.e. small enough to give useful information of the function of a limited area of the underlying cerebral cortex.

3. The transynaptic effects of axons directly excited by TMS.

The axons that are directly excited by TMS may transynaptically act 3.1 distantly or 3.2 locally.

(3.1) Distant Effects

These are typically exerted transynaptically on alpha motoneurons, which permits a wide variety of procedures including: (a) estimation of central motor conduction time and its alteration in demyelinating disorders, strokes, amyotrophic lateral sclerosis (ALS), with programs of TMS stimulation in rehabilitation etc. (b) Mapping muscle representation and demonstrating plasticity after brain and spinal cord damage. (c) Intraoperative motor monitoring to warn of possible impending damage during spinal cord, brainstem and cerebral cortical surgery.

Currently, TMS is much less employed in monitoring

connections between brain areas as revealed by evoked potential recording from an area of cerebral cortex following focal TMS of a homotopic area on the opposite hemisphere [12], or from cerebellum to frontal lobe [13]. The inhibitory effect on motor cortical output by TMS of the opposite hemisphere [14] or the contralateral cerebellum [15] reveal an important physiological action of such connectivities.

(3.2) Local Effects

Unfortunately, intracellular recordings have not been obtainable within a few mm of a discharging TMS coil. Nevertheless, intracellular recordings of the neuronal response to a brief electrical pulse applied to the pial surface of motor cortex provide a clue to the local effects of TMS. An electrical pulse may directly excite a CT neuron, or a motor cortical neuron not so labeled, or may excite afferent fibers that generate an EPSP sufficient or insufficient to reach firing level for an action potential. A few ms later, a prolonged IPSP occurs ending for >50ms further evoked or ongoing discharge by the neuron [16]. The sequence if EPSP, action potential discharge, then IPSP with neuronal silence implies either a network property with inhibitory feedback by collaterals of the discharging neuron, or the effects of mixed direct activation of excitatory and inhibitory afferent axons.

Fortunately, discharges of CT fibers and their effects on alpha motoneurons can be monitored in animals and humans; combined with physiological analytical techniques, the events within the "black box" of the motor cortex can be deduced from the output system (reviewed in [17]. A TMS coil oriented to induce a P-A electric field in motor cortex (or parietal lobe) causes a sequence of synchronized, postsynaptic discharges, termed indirect (I) waves, I_1, I_2, I_3 to descend the CT. The I_1 wave depends on monosynaptic activation of large motor cortical CT neurons followed by repetitive discharge about 1.5 ms later in the same CT neurons, or others initially discharge. The population of CT neurons thus exhibits, especially in higher mammals, (e.g. monkeys and humans) a remarkably stereotyped high frequency (˜600 Hz) discharge pattern that is suggestive of a "clock-like" function [17]. Confirmation was recently obtained that 600 H_z (˜1.5 ms periodicity) also can be retrieved by point processing physiological activity, i.e. it is not an artifact restricted to TMS. Thus, the ensemble of several motor unit discharges in extrinsic laryngeal muscles during silent articulation of plosive consonants displays 1.5 ms components. Probably the short peripheral motor conduction time (˜ 2 ms) and the precision of central computation in speech production aided such finding [18]. Such a clock function would be appropriate in the motor cortex in signaling through CT neurons the exquisite coordination of angular velocities at multiple limb joints that secures a straight line trajectory of the forefinger to a target. The motor cortical network that is responsible for the multiple I waves has been investigated by the standard physiological techniques of intracortical stimulation with microelectrode and progressive cooling of motor cortex from the surface. Apparently, the network is vertically oriented such that late I waves depend on the superficial motor cortical layers activating the CT neurons located in the deeper layers. Thus, provided the direct (D) latency is first established by TMS in the L-M orientation, the P-A orientation has major utility in exploring the synaptic networks of cerebral cortex in health and possibly in degenerative cerebral conditions such as Alzheimer disease.

4. The effects of repetitive versus single(s) TMS pulses.

Initially, the effects only of sTMS pulses could be investigated. However, within a few years two methods of repetitive TMS stimulation became available; either 2-4 sTMS generators could be linked to a single coil or a repetitive stimulator, with the capability of providing long trains of stimuli, which might require cooling of the coil even at the limited frequencies available, usually not exceeding 50 H_z.

(4.1) Linked sTMS stimulation

Kujirai et al [19] introduced a powerful method of eliciting inhibition in motor cortex; when a subthreshold TMS pulse preceded a test suprathreshold TMS pulse by an interval of 1-6 ms the test response was markedly inhibited. At increased test intervals (10-15 ms), facilitation was elicited. The two TMS pulse paradigm was extensively used to analyze a variety of neurological disorders, with the finding usually of diminished inhibition. A recent extension of the inhibitory paradigm, using two subthreshold TMS pulses preceding the test suprathreshold TMS pulse, revealed enhanced inhibition, but no evidence of 1.5 ms periodicities that would evidence an interneuronal network resembling that for I waves [20].

Changing the TMS stimulus parameters such that two just above threshold stimuli were tested revealed marked facilitation at interstimulus intervals ˜1.5 ms and its multiples [21]. Such finding supported the existence of an excitatory interneuron circuit generating the I wave periodicity. Unexpectedly, when the test stimulus intensity was reduced to e.g. 75% of the near threshold conditioning stimulus and delayed 1.2 ms i.e. within the relative refractory period of the afferent axons excited by the conditioning stimulus, facilitation was clearly apparent [22,23]. At a test delay of 1.2 ms, the brief membrane time constant of myelinated afferent fibers would preclude facilitation from residual facilitation at the node. However, residual EPSPs from the conditioning stimulus could permit depolarization by even a weak test stimulus to reach firing level. Thus, with two or more TMS stimuli, the site of lowest threshold excitation need no longer be at the myelinated fiber, but could be closer to the neuronal cell body.

(4.2) Long train repetitive TMS stimulation

The advantage of using long train TMS stimulation is the enhanced but reversible inhibition of an area of cortex; the major disadvantage is the loss of precise timing of cerebral cortical change, easily attainable with linked STMS stimulation. Furthermore, the danger of eliciting a seizure, either in a normal subject or a patient, requires that close attention be paid to the parameters of stimulation. Repetitive trains were first tested on cerebral cortical processing of language symbols (reviewed in [24]. A major clinical use was the extension of repetitive TMS to the alleviation of depression by subconvulsive repetitive TMS of the left prefrontal cortex [25]. A final decision of its efficacy is still awaited. It is noteworthy that the standard choice of a figure 8 coil for such repetitive TMS may be unfortunate because the optimal orientation of the induced electric field is unclear. Such treatment might well improve if the TMS train were directed through a cooled small (e.g. 6 cm) round coil over the cortical area.

References

[1] W. Penfield and L. Roberts, "Speech and brain mechanisms," Princeton, Princeton University Press, 1959.

[2] P.A. Merton and H.B. Morton , "Stimulation of the cerebral cortex in the intact human subject," Nature vol. 285, pp. 227, 1980.

[3] A.T. Barker, R. Jalinous and I.L. Freeston, "Non-invasive magnetic stimulation of the human motor cortex," *Lancet* vol. I, pp. 1106-1107, 1985.

[4] V.E. Amassian, R.Q. Cracco and P.J. Maccabee, "Focal stimulation of human cerebral cortex with the magnetic coil: A comparison with electrical stimulation," *Electrocenceph. Clin. Neurophysiol.* vol. 74, pp. 401-416, 1989.

[5] V.E. Amassian, M. Somasundaram, J.C. Rothwell, T. Britton, J.B. Cracco, R.Q. Cracco, P.J. Maccabee and B.L. Day, "Paraesthesias are elicited by single pulse, magnetic coil stimulation of motor cortex in susceptible humans," Brain vol. 114, pp. 2505-2520, 1991.

[6] A.T. Barker, C.W. Garnham and I.L. Freeston , "Magnetic nerve stimulation: the effect of waveform on efficiency, determination of neural membrane time constants and the measurement of stimulator output," in *Magnetic motor stimulation: basic principles and clinical experience,* suppl. 3, W.J. Levy, R.Q. Cracco, A.T. Barker, J. Rothwell, Eds. New York:Elsevier Scientific B.V., 1991, pp. 227-248.

[7] J.C. Rothwell, B.L. Day and V.E. Amassian, "Near threshold electrical and magnetic transcranial stimuli activate overlapping sets of cortical neurons in humans," *J. Physiol. (Lond),* vol. 452, pp. 109p, 1992.

[8] W.A.H. Rushton, "Effect upon the threshold for nervous excitationon the length of nerve exposed and the angle between current and nerve," *J. Physiol (Lond.)*, vol. 63, pp.357-377.

[9] P.J. Maccabee, V.E. Amassian, L.P. Eberle and R.Q.Cracco, "Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerve in-vitro: locus of excitation," *J. Physiol. (Lond.)*, vol. 460, pp. 201-219.

[10] V.E. Amassian, L. Eberle, P.J. Maccabee and R.Q. Cracco, "Modeling 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," *Electroenceph. Clin. Neurophysiol.,* vol. 85, pp. 291-301, 1992.

[11] V.E. Amassian, P.J. Maccabee, R.Q. Cracco, J.B. Cracco, M. Somasundaram, J.C. Rothwell, L. Eberle, K. Henry and A.P. Rudell, "The polarity of the induced electric field influences magnetic coil inhibition of human visual cortex: implications for the site of excitation," *Electroenceph. Clin. Neurophysiol.,* vol. 93, pp. 21-26, 1994.

[12] R.Q. Cracco, V.E. Amassian, P.J. Maccabee and J.B. Cracco, "Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation," *Electroenceph. Clin. Neurophysiol.* vol. 74, pp. 417-424, 1989.

[13] V.E. Amassian, R.Q. Cracco, P.J. Maccabee and J.B. Cracco, "Cerebello-frontal cortical projections in humans studied with the magnetic coil." *Electroenceph. Clin. Neurophysiol.,* vol. 95, pp. 265-272, 1992.

[14] A. Ferbert, A. Priori, J.C. Rothwell, B.L. Day, J.G. Colebatch and C.D. Marsden, "Interhemispheric inhibition of the human motor cortex," *J. Physiol. (Lond).,* vol. 453, pp. 525-546, 1992.

[15] Y. Ugawa, Y. Uesaka, Y. Terao, R. Hanajima and I. Kanazawa, "Magnetic stimulation over the cerebellum in humans," *Ann Neurol.,* vol. 37, pp. 703-713, 1995.

[16] J. Rosenthal, H.J. Waller and V.E. Amassian, "An analysis of the activation of motor cortical neurons by surface stimulation," *J. Neurophysiol.,* vol. 30, pp. 849-858, 1967.

[17] V.E. Amassian and M. Stewart, "Motor cortical and other interneuronal networks that generate very high frequency waves," in *Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation*,", suppl. 56, W. Paulus, F. Tergan, M.A. Nitsche, J.C. Rothwell, U. Zeimann, M. Hallet, Eds. *Clin. Neurophysiol,* 2003, pp. 119-142.

[18] V.E. Amassian, M. Stewart, L. Eberle, R.Q. Cracco and P.J. Maccabee, "Human EMGs have a 600 H_z component (I wave periodicity) during articulation, *J. Physiol. (Lond.),* vol.. 555P, 2004.

[19] T. Kujirai, M.D. Caramia, J.C. Rothwell, B.L. Day, P.D. Thompson, A. Ferbert, S. Wroe, P. Asselman and C.D. Marsden, "Corticocortical inhibition in human motor cortex," *J. Physiol.,* vol. 471, pp. 501-519, 1993.

[20] S. Bestmann, H.R. Siebner, N. Modugno, V.E. Amassian and J.C. Rothwell, "Inhibitory interactions between pairs of subthreshold conditioning stimuli in the human motor cortex," *Clin. Neurophysiol,* vol. 115, pp. 755-764, 2004.

[21] H. Tokimura, M.C. Ridding, Y. Tokimura, V.E. Amassian and J.C. Rothwell, "Short latency facilitation between pairs of threshold magnetic stimuli applied to human motor cortex," *Electroenceph. Clin. Neurophysiology,* vol. 101, pp. 263-272, 1996.

[22] V.E. Amassian, J.C. Rothwell, R.Q. Cracco, P.J. Maccabee, M. Vergara, N. Hassan and L. Eberle, "What is excited by near-thershold twin magnetic stimuli over human cerebral cortex?, *J. Physiol. (Lond.),* vol. 506.P, pp. 122P, 1998.

[23] U. Ziemann, F. Tergau, E.M. Wassermann, S. Wischer, J. Hilderbrandt and W. Paulus, "Demonstration of facilitatory I-wave interaction in the human motor cortex by paired transcranial magnetic stimulation," *J. Physiol. (Lond.),* vol. 511, pp. 181-190, 1998.

[24] V.E. Amassian, R.Q. Cracco, P.J. Maccabee, J.B. Cracco, A.P. Rudell and L. Eberle, "Transcranial magnetic stimulation in the study of the visual pathway," *J. Clin. Neurophysiol.,* vol. 15, pp. 288-304, 1998.

[25] M.S. George, E.M. Wassermann, W.A. Williams, A. Callahan, T.A. Ketter, P. Basser, M. Hallett and R.M. Post, "Daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) improves mood in depression," *Neuroreport*, vol. 6, pp. 1-6, 1995.