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REVIEW

State of the art: Physiology of transcranial motor cortex stimulation

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Summary

The motor cortex can be stimulated transcranially producing excitatory and inhibitory phenomena in muscles controlled by the activated cortical areas. The physiologic bases of these effects are still relatively poorly understood because of the complexity of the interactions between the currents induced in the brain with an intricate arrangement of neural circuits in the cerebral cortex, which is composed of multiple excitatory and inhibitory networks of cell bodies and axons of different size, location, orientation and function. All forms of stimulation of the intact motor cortex tend to produce repetitive discharge of corticospinal neurones; however, different structures of these central motor circuits seem to be preferentially targeted by the available different techniques of stimulation. Direct recording of the evoked corticospinal output has provided important insight into the excitatory and inhibitory phenomena produced by cerebral cortex stimulation. An updated overview of human and animal studies on the physiologic mechanisms of intact motor cortex stimulation is presented.

Keywords motor cortex; transcranial stimulation; I waves; pyramidal cell; corticospinal system

The noninvasive techniques of transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) have enormously advanced our knowledge of the human motor system. It is important to stress that the cerebral cortex is a complex structure composed of excitable elements (cell bodies and axons) that vary in size, location, orientation, and function: all of these variables will influence their response to TMS or TES. A second important point is that although TMS and TES can be used to probe, to facilitate, and to suppress or inhibit the cortical network, these tools are artificial and neither is able to imitate in full the engagement of the same network that occurs during a voluntary movement.

Initial studies in animals have shown that in response to a single electrical stimulus to the motor cortex, an electrode placed in the medullary pyramid or on the dorsolateral surface of the cervical spinal cord records a series of high-frequency waves.[1-3] The earliest wave that persisted after cortical depression and after cortical ablation was thought to originate from the direct activation of the axons of fast

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pyramidal tract neurones (PTN) and was therefore termed the "D" wave. The term PTN is loosely exchangeable for corticospinal neurone (CSN), because most PTNs project their axons into the spinal cord as the corticospinal tract (CST). The later waves excited by cortical stimulation required the integrity of the cortical grey matter and were thought to originate from indirect, trans-synaptic activation of PTNs and were therefore termed "I" waves.[2] Recordings from individual PTN axons showed that a given axon may produce both a D and a subsequent I wave discharge.[2]

Direct evidence for the action of TMS and TES on the human motor cortex was initially provided by recording from the surface of the spinal cord during spinal cord surgery.[4-7] Although these results were very useful, interpretation was limited because the patients were anesthetized. More recently, descending volleys have been recorded in conscious human subjects with no central nervous system (CNS) abnormality who had electrodes implanted in the spinal cord for the relief of otherwise intractable pain.[8-11] These recordings provide detailed insights about the physiologic basis of the excitatory and inhibitory phenomena produced by single, paired, and repetitive transcranial stimulation of the human brain.

Direct recording of the output of the motor cortex showed that transcranial stimulation can evoke several different kinds of descending activities depending on the type of stimulation: magnetic or electrical, and, in the case of magnetic stimulation, on the direction of the induced current in the brain, the intensity of the stimulus, the phases of the stimulating current (monophasic or biphasic), and the shape of the coil.[11] The output also depends on which region of the motor cortex is stimulated (upper or lower limb area).[11]

Animal studies

The advent of noninvasive TMS in the 1980s generated a great deal of interest in how they act on the brain's motor network. There are some very clear historical parallels with direct electrical stimulation of the brain of experimental animals and, indeed, of human patients, work that goes right back to the time of Ferrier, Horsley, Sherrington, and Penfield. The action of electrical stimuli on a complex organ such as the cerebral cortex is not simple and we still do not fully understand how TMS works. Nevertheless, it has been possible to use the concepts and models generated by work on experimental animals to help explain many of the basic actions of TMS.[12,13]

Electrical stimulation of the motor cortex

Most relevant to this review are the actions of brief electric (0.1-10 milliseconds) pulses on the cortex. These are either delivered through a ball electrode on the cortical surface or through an intracortical electrode positioned at different depths with the grey matter. In a monopolar montage, there is a remote or indifferent (return) electrode. If the pulse is delivered through two closely spaced electrodes, it is referred to as bipolar stimulation. Current pulses can be either monophasic, the active electrode is the cathode (negative) under which there is depolarization of neural elements, whereas hyperpolarization occurs at the remote (positive) indifferent electrode, or vice versa for anodal stimulation. Alternatively, biphasic pulses can be used, with a brief interval between them. The duration of pulses is selected according to the characteristics of the elements being stimulated.[14]

All forms of electrical stimulation of the intact motor cortex tend to produce repetitive discharge of CSNs, as first demonstrated by Patton and Amassian.[2] Phillips et al[15] showed that by using relatively long (5-10 milliseconds) surface anodal pulses in a monopolar configuration, it was possible to generate a relatively pure D-wave in the baboon CST, probably from CSNs located on the convexity of the precentral gyrus and beneath the active electrode. These neurons have their long axes at right angles to the cortical surface: in this case, a surface anode induces inward current in the apical dendrites close to the surface and outward (cathodal) current through the axon, initiating a D-wave in the axon. It is worth remembering that much of the classical area 4 in the human cortex is buried in the anterior bank of the central sulcus,[16] in which most CSNs would have their long axes lying parallel to the cortical surface.

It is possible to calculate the physical spread of stimulating currents within the cortex, because this is related to the known electrical characteristics of the tissue.[14] However, the *physiologic* spread, caused by the activation of intracortical synapses, is much more difficult to assess, but is probably quite considerable, even for methods that are described as "focal." The repetitive activation caused even by single shock electrical stimulation of the cortex will induce temporal summation at many synapses and discharge of postsynaptic elements, enhancing the extent of physiologic spread.[17,18] For example, late I waves in CSNs originating in the M1 hand area can arise from stimulation of the ventral premotor area.[19,20]

Characteristic actions of TMS on primate CSNs

Epidural recordings in humans have given us many insights into the actions of TMS in humans (described later in this text). However, we have limited information on its action on single neurones. Such information is important because of variation in the function of different CSNs: they originate from different regions of the cerebral cortex, have a wide variety of sizes and types, and exert different postsynaptic actions on a range of spinal targets.[21] Some insights into the cortical action of TMS were obtained in a