Transcranial Magnetic Stimulation: Foundational Techniques for Aeromedical Research

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This column is coordinated and edited by Valerie E. Martindale, Ph.D. These articles are not peer-reviewed. The AsMA Science and Technology Committee provides the Watch as a forum to introduce and discuss a variety of topics involving all aspects of civil and military aerospace medicine. Please send your submissions and comments via email to: vemartindale@hotmail.com. Watch columns are available at www.asma.org through the "Read the Journal" link.

In recent years, noninvasive neurostimulation techniques, such as transcranial magnetic stimulation (TMS), have grown in popularity in both clinical practice and neuroscience research. For example, medical professionals use repetitive TMS to induce long-lasting plasticity in the brain, which can treat neurological and psychiatric conditions such as major depressive disorder, obsessive compulsive disorder, and migraine headaches.[5] In contrast, researchers use protocols such as single-pulse TMS and paired pulse TMS (ppTMS), which are thought to have short-term effects on brain function. These protocols are used to map sensory, motor, and cognitive brain function, explore the excitability of brain regions under variable conditions, and study the links between the brain and observable behavior.[12] Here, we provide a foundation for understanding TMS and examples of potential research applications to the fields of aerospace medicine and human performance. This discussion is especially important as TMS offers unique advantages that are not available by the study of behavior alone or through neuroimaging techniques such as functional magnetic resonance imaging or electroencephalography—specifically, the ability to both influence and measure brain function in a noninvasive manner.

Mechanisms of Action

Using the basic principles of electromagnetic induction (Faraday's law of induction), it is possible to noninvasively activate a small area of neurons in the brain. TMS works by quickly passing current through an insulated wire coil held above the scalp, generating a strong enough magnetic field to induce a small transient eddy current in the underlying neural tissue. This eddy current acts on any electrically excitable cells within small superficial areas of tissue, such as neurons in the brain. If sufficient, the voltage causes membrane depolarization, resulting in action potentials that propagate along the nerve. Activity will spread to any connected circuitry and activate synaptic mechanisms, including neurotransmitter release and plasticity. In short, TMS is a noninvasive method that can directly cause action potentials. This activity will propagate along axon membranes and transmit information between neurons in a manner similar to naturally occurring action potentials.

Safety Considerations

The consensus from the neurostimulation community is that single-pulse TMS and ppTMS can be performed safely in most individuals, whereas repetitive TMS carries a very small seizure risk that has been safely overcome by proper guidelines on dosing.[9,10] Contraindications for TMS are similar to magnetic resonance imaging and include the presence of ferromagnetic material or any implanted electronic or medical devices that could be affected by the electromagnetic field. There is no known history of seizure with single or paired pulse TMS in healthy individuals and reported adverse effects are limited to local discomfort and headache.

What Can Be Measured?

In its most basic form, TMS is applied to the motor cortex (M1), often to the hand region due to its large, easily targetable size, while responses at the muscle are measured (**Fig. 1**). If the TMS pulse is of sufficient intensity, corticospinal neurons in M1

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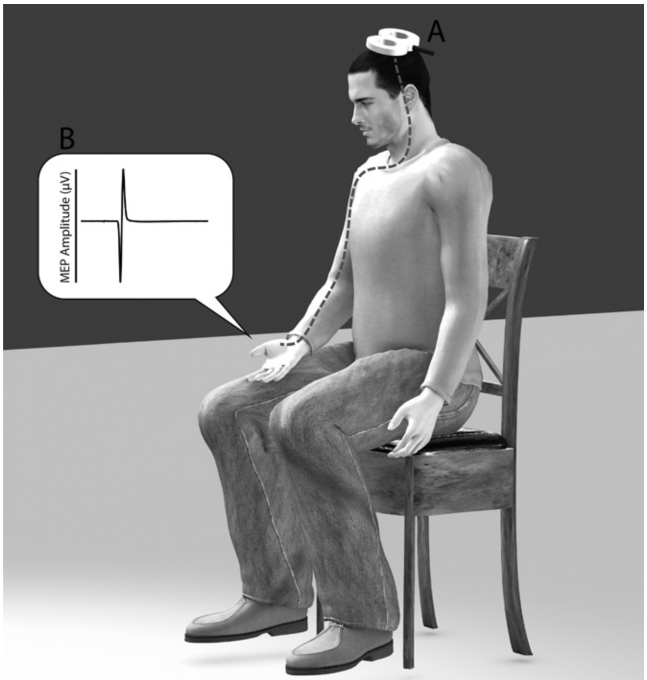

Fig. 1. Motor pathway activity is initiated by a magnetic pulse delivered by a TMS coil to the hand region of the motor cortex (A). If of sufficient intensity, a propagation of impulses travels through upper and lower motor neurons (dashed line) to the corresponding hand muscles. The amplitude of the TMS-induced MEP (B) recorded by surface EMG electrodes on the hand muscles reflects excitability within the motor pathway.

become activated. When activated, these neurons send a descending volley of action potentials down the corticospinal tract toward the corresponding muscles, causing a brief twitch—a quantifiable response referred to as a motor evoked potential (MEP). This MEP is recorded with surface electrodes used for electromyography (EMG) and used to calculate basic TMS measurements like motor threshold, latency, and size of the MEP. These measurements are related to the number of motor neurons activated in the muscle, the magnitude and synchronization of the descending neuronal volley from the brain, and the brain's excitability—all of which may be influenced by environmental and participant characteristics. Here, we review a few common TMS measures used in research, each of which provides unique information about the neurophysiology of the central nervous system.

Motor threshold. Motor threshold (MT) refers to the stimulation intensity of TMS required to produce a motor response (MEP in the target muscle). The threshold for producing a MEP is predominantly a measure of membrane excitability in the cortico-cortical and thalamo-cortical fibers.[2] MT varies across individuals but is remarkably consistent in any given individual over time. This known consistency suggests that MT is a promising TMS metric for both longitudinal research as well as transient changes due to the environment, pharmacokinetics (such as medications that alter sodium and calcium channels), or participant characteristics, as just a few examples.

Paired pulse TMS. Paired pulse TMS (ppTMS) involves applying two TMS pulses to either study intracortical inhibition or facilitation, depending on the intensity and timing of the pulses. A 'conditioning' stimulus produces a relatively consistent temporal pattern of excitatory and inhibitory events that can be timed in relation to a 'test' stimulus to modulate the amplitude of the MEP produced by the test stimulus. Inhibition protocols can attenuate a normal motor response, while facilitation protocols can augment the normal response. By comparing to the normal response, ppTMS protocols are thought to offer the ability to quantify excitatory and inhibitory neurotransmission events in the stimulated circuitry. In the short-term, ppTMS protocols are known to be stable within individuals,[1] but can change with age,[7] sleep wake cycles,[11] or medication use,[3] as a few examples.

Cortical silent period. Cortical silent period (cSP) refers to the brief inhibition of voluntary muscle contraction that occurs when TMS is given during active contraction of the target muscle. cSP is influenced by short-term spinal inhibitory mechanisms ($<$ 50 ms) and longer lasting inhibition originating within the motor cortex (up to 300 ms). cSP is a general measure of cortico-cortical inhibition and has been shown to change during periods of hyperventilation[8] and major depressive disorder,[6] as examples.

Recruitment curve. Recruitment curves (RCs) use single-pulse TMS over a range of intensities both above and below the individual's MT. This produces an input-output response curve that is sigmoidal in shape—as higher intensities are used, larger muscle twitches are evoked until a maximum response (plateau) is reached. RC parameters, such as area under the curve and slope, can provide detailed information about the corticospinal tract pathways being stimulated. RCs can be measured while the participant is resting, or during a sustained muscle contraction. Resting RCs activate lower threshold neurons, while active RCs reflect higher threshold neurons, which may have different functional significance.[4]

Potential TMS Aerospace Applications

Although a thorough discussion is beyond the scope of this brief introduction, example applications of TMS in aerospace include longitudinal research to explore the effects of prolonged exposure to microgravity, bedrest, or the effects of high- or low-pressure environments on neurophysiology. Further, TMS may show promise in the study of the neurophysiological effects of nutrition, hydration status, lifestyle, fatigue, circadian disruption, medical treatments, antecedents, pharmacokinetics, or even broad information about phenotype. In summary, a comprehensive TMS paradigm using all of the measures described here can be implemented in a single session, and offers the potential to answer diverse hypothesis-driven research questions and examine the neurophysiology of the central nervous system in response to many issues of concern to aerospace medicine.

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Erratum

Regarding: Alkner BA, Bring DK-I. *Muscle activation during gravity-independent resistance exercise compared to common exercises.* Aerosp Med Hum Perform. 2019; 90(6):506–512. DOI: https://doi.org/10.3357/AMHP.5097.2019.

In Table I, the SD value for FW Ecc Peak Force value should be 748 (and not 7489). The EMG data are not affected by this and it does not affect the results, discussion, or conclusion of the paper. The corrected table is printed below. We apologize for any inconvenience this may have caused.

Table I. Average Torque, Force and 10 RM Values.

10-RM WEIGHT	AVERAGE VALUE
MVC Pre, Peak Torque (Nm)	487 (98)
FW Con, Peak Force (N)	3527 (818)
FW Ecc, Peak Force (N)	2632 (748)
LP, 10 RM load (kg)	245 (67)
FS,10 RM load (kg)	92 (26)
ID Con, Peak Torque (Nm)	349 (112)
ID Ecc, Peak Torque (Nm)	511 (145)
KE,10-RM load (kg)	43 (9)
MVC Post, Peak Torque (Nm)	452 (84)

Peak torque, peak force, and 10-RM weight values for the different exercises. Values are mean (SD) for eight subjects. MVC = Maximal voluntary contraction, isometric knee extension; FW = flywheel leg press; FS = front squat with barbell; ID = knee extension in an isokinetic dynamometer; KE = knee extension in a weight stack machine; LP = leg press in a weight stack machine; Con = concentric; Ecc = eccentric.