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Transcranial magnetic stimulation: Neurophysiological applications and safety

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Abstract

TMS is a non-invasive tool for measuring neural conduction and processing time, activation thresholds, facilitation and inhibition in brain cortex, and neural connections in humans. It is used to study motor, visual, somatosensory, and cognitive functions. TMS does not appear to cause long-term adverse neurological, cardiovascular, hormonal, motor, sensory, or cognitive effects in healthy subjects. Single-pulse (<1 Hz) TMS is safe in normal subjects. High frequency, high-intensity repetitive TMS (rTMS) can elicit seizures even in normal subjects. Safety guidelines for using rTMS have been published.

Keywords: Transcranial magnetic stimulation; Human neurophysiology; TMS; rTMS; Motor; Cognition; Vision

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive, relatively painless method to activate or suppress human motor cortex and motor control, visual cortex and perception, somatosensory inputs, cerebellar systems, and cognitive processing. To deliver TMS to the brain, an electrical current is run through a round coil of wire placed over the scalp. This current generates a transient magnetic field carried through the scalp, skull, and meninges to the underlying cortex. An electrical current is thereby induced in a cortical region whose volume depends on coil shape and size, magnetic field strength (intensity), and frequency and duration of magnetic pulses delivered. TMS can either activate or suppress motor, sensory, or cognitive functions, depending on the brain location and parameters of its delivery. Coil location is guided by head and brain imaging data or by the international 10–20 electrode placement system (Homan, Herman, & Purdy, 1987).

TMS provides a powerful method for measuring neural conduction and processing time, activation thresholds, facilitation and inhibition in brain cortex, and

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neural connections. By activating or inhibiting function, it can help identify brain regions instrumental in specific tasks. Its high temporal resolution allows the timing of their involvement to be determined. Another investigative strategy is to use TMS to create a physiologic "lesion" that simulates brain lesions in patients to test hypotheses about functional anatomy.

TMS can be used in conjunction with brain imaging techniques for a variety of purposes. For example, magnetic resonance imaging (MRI)-to-head coregistration of functional imaging anatomy can guide TMS coil location to regions of interest where physiologic functions and their timing can be assessed. TMS can also provide functional and temporal information about the neural activity associated with the localized hemodynamic changes measured with functional magnetic resonance imaging (fMRI) (Bastings et al., 1998; Boroojerdi et al., 1999) or regional cerebral blood flow (rCBF) as measured by positron emission tomography (PET) (Paus et al., 1997; Paus et al., 1998). PET can measure not only the local effects on rCBF at the site of focal TMS, but also distal changes that reflect connectivity with the stimulated brain area (Ferbert et al., 1992; Paus et al., 1997, 1998; Siebner et al., 2001). Similarly, functional brain imaging performed before and after repetitive TMS (rTMS) can be used to assess the long-term effects of rTMS on the brain (Paus, 1999). Combining TMS with functional brain imaging is therefore a promising strategy for investigating human brain systems neurophysiology.

TMS can topographically map human motor cortex, but its optimal position accuracy on the order of a centimeter or two is poor compared to the millimeter spatial resolution of fMRI (Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992). Moreover, TMS produces both local and remote electrophysiological effects (Gerschlager, Siebner, & Rothwell, 2001; Ilmoniemi et al., 1997; Jing & Takigawa, 2000; Paus et al., 1997, 1998). fMRI is therefore superior to TMS in demonstrating functional human neuroanatomy.

Magnetic stimulators typically induce maximum magnetic field strengths with an upper limit of approximately 2 T. The duration of a single pulse of TMS is less than 1 ms, while a train of pulses applied during rTMS spans a longer duration. When TMS is delivered through a round coil, the induced electrical field is maximal under the circular rim of the coil and less in the center of the coil (Cohen et al., 1990; Roth, Saypol, Hallett, & Cohen, 1991). When TMS is delivered through a figure-eight or butterfly-shaped coil, the induced electrical field is maximal under the center of the coil, allowing fairly focal brain stimulation. Models of electrical fields produced by TMS have been used to estimate the size of the electrical field created in the brain with different types of coils (Cohen et al., 1990; Roth et al., 1991). The magnitude of the TMS-induced electrical field for any coil decreases as a function of brain depth below the coil.

The ethical issues associated with the use of TMS in humans primarily pertain to risk and safety concerns, which vary by protocol. For example, single pulses of TMS delivered at a frequency of less than 1 Hz at a high magnetic field strength are considered safe, while high-intensity rTMS can involve risk to a subject. In this report, we selectively summarize different neurophysiological applications of single-pulse, paired-pulse, double-coil, and rTMS and the information available about their safety in adults. Clinical diagnostic and therapeutic studies with TMS and the biophysics of TMS have recently been reviewed elsewhere (Mills, 1999).

2. Single-pulse TMS

TMS delivered to motor cortex as a single pulse with a frequency less than 1 Hz was the first and most widely used method for studying human brain neurophysiology (Barker, Jalinous, & Freeston, 1985). The technique was subsequently applied

Table 1
Investigative uses of single-pulse, paired-pulse, and double-coil TMS

Motor systems
Cortical activation threshold
Central motor conduction time
Topographic mapping of evoked motor potentials
Cortical plasticity/reorganization
Silent period inhibition
Modulates volitional movement
Intracortical inhibition and facilitation
Transcallosal inhibition of homotopic cortex
Cerebellar inhibition of motor cortex
Modulates saccade initiation
Visual systems
Topographic mapping of evoked phosphenes
Cortical activation threshold
Suppresses perception
Prolongs occipital cortex processing time
Topographic mapping of scotoma
Feedforward occipital to extrastriate conduction time
Modulates extrastriate visual feedback to occipital cortex
Somatosensory systems
Suppresses perception
Suppresses stimulus localization
Sensorimotor integration and cognition
Disrupts memory-guided saccade preparation
Disrupts eye–hand coordination
Increases reaction time in attention and working memory tasks
Modulates pseudoneglect

to the study of the human visual system and cognition. Table 1 summarizes the neurophysiological uses of single-pulse TMS, as well as paired-pulse and double-coil TMS.

2.1. Motor cortex and systems

A single pulse of high-intensity TMS delivered to primary motor cortex readily evokes motor potentials from the resting contralateral upper extremity, providing a means of measuring the threshold for exciting a population of motor cortex neurons and for determining central motor conduction time. The amplitude of the motor evoked potential increases as TMS intensity increases. The activation of these motor potentials is facilitated by volitional contraction of upper extremity muscles or by imagining or observing their volitional contraction. As the force of volitional contraction of the distal arm muscle increases, the TMS intensity necessary to excite motor cortex neurons decreases and regional cerebral blood flow increases logarithmically in the contralateral motor cortex (Dettmers et al., 1996). The lowest TMS intensity necessary to excite a population of motor cortex neurons increases as the distance between coil location and motor cortex increases, as measured by MRI (McConnell et al., 2001).

Motor cortex topography for the hand, proximal arm, and face can be mapped with a figure-eight stimulating coil (Brasil-Neto et al., 1992). A single pulse of TMS delivered in the region of the frontal eye fields, however, does not evoke saccadic eye movements (Barker et al., 1985; Li, Olson, Anand, & Hotson, 1997; Müri, Hess, & Meienberg, 1991; Wessel & Kompf, 1991). The peak motor evoked responses of TMS topographic maps are coincident with the peak fMRI activation. Both techniques also show a parallel shift in peak motoneuron density or motor activity with brain

reorganization (Boroojerdi et al., 1999; Krings et al., 1997a; Macdonell et al., 1999). Topographic maps obtained using TMS are also coincident with those obtained using cortical electrical stimulation (Krings et al., 1997b).

Single pulses of TMS can not only activate motor cortex, but can also produce inhibitory responses from motor cortex. If a subject voluntary contracts a muscle with repetitive electromyograph discharges prior to TMS being delivered to motor cortex, the evoked motor potential is followed by a pause in the ongoing background electromyography activity. This pause, or silent period, typically lasts at least 50–100 ms and increases as TMS intensity increases. The silent period may in part reflect intracortical inhibition (Cantello, Gianelli, Civardi, & Mutani, 1992; Uncini, Treviso, Di Muzio, Simone, & Pullman, 1993; von Giesen, Roick, & Benecke, 1994). Single-pulse TMS of motor cortex also perturbs the neural circuits that initiate motor programs, as reflected by delays in the execution of volitional limb and saccadic eye movements (Day et al., 1989; Priori, Bertolasi, Rothwell, Day, & Marsden, 1993; Ro, Cheifet, Ingle, Shoup, & Rafal, 1999; Schluter, Rushworth, Mills, & Passingham, 1999; Schluter, Rushworth, Passingham, & Mills, 1998; Terao et al., 1998; Thickbroom, Stell, & Mastaglia, 1996; Ziemann, Tergau, Netz, & Homberg, 1997).

2.2. Visual cortex and sensory systems

A single pulse of TMS delivered to the occipital pole can either activate or suppress neural processes. If subjects are placed in darkness or close both eyes, TMS delivered over occipital cortex can evoke stationary phosphenes (Marg & Rudiak, 1994; Pascual-Leone & Walsh, 2001). The threshold intensity for eliciting phosphenes provides a measure of occipital cortex excitability, though it is more variable within subjects than the intensity for activating motor cortex, and it is not correlated with this intensity (Stewart, Walsh, Frith, & Rothwell, 2001a). Furthermore, phosphene thresholds are reduced and fMRI activation by photic stimulation is increased after 60 min of light deprivation (Boroojerdi et al., 2000a).

TMS delivered over occipital cortex at a higher intensity, above the phosphene threshold, transiently suppresses perception of a visual stimulus when delivered in a discrete time window (Amassian et al., 1989; Beckers & Homberg, 1991). This suppression allows the timing of visual processing to be determined. Amassian et al. (1989) found that TMS delivered to occipital cortex 80–100 ms after a brief display of three letters reduces accuracy of letter discrimination, while TMS delivered at shorter or longer latencies has a weaker or no effect on accuracy. Positioning the coil off the occipital midline degrades perception in the contralateral visual field. Furthermore, TMS delivered more focally through a butterfly coil can create discrete, topographic scotoma (Kamitani & Shimojo, 1999).

The loud auditory click that accompanies a TMS pulse activates primary auditory cortex (Nikouline, Ruohonen, & Ilmoniemi, 1999; Siebner et al., 1999) and therefore limits its use in studying human auditory cortex. Stimulation of somatosensory cortex does not reliably elicit paresthesia, but it can block perception of electrical stimulation of the fingers and localization of the stimulus site (Cohen, Bandinelli, Sato, Kufta, & Hallett, 1991; Seyal, Siddiqui, & Hundal, 1997).

2.3. Higher cognitive processing

Single-pulse TMS has been less effective than higher frequency rTMS in investigating higher cognitive processes such as language, memory, and attention. It has, however, demonstrated neuroplasticity associated with learning or practicing motor skills. Implicit learning of a serial reaction time task is correlated with progressive enlargement of the maps of cortical outputs to muscles involved in the task (Pascual-Leone, Grafman, & Hallett, 1994a). When subjects become aware of the

task requirements (explicit knowledge), then the enlarged motor output maps return to their baseline size prior to implicit learning. This finding suggests involvement of brain structures other than motor cortex once implicit motor learning becomes explicit knowledge. Motor maps also increase, and motor activation thresholds decrease, as novices physically or mentally practice and learn piano sequences (Pascual-Leone et al., 1995).

Classen et al. further demonstrated motor cortex neuroplasticity by having subjects practice a thumb movement that was in the opposite direction of a thumb movement evoked by TMS delivered over primary motor cortex. This motor practice temporarily shifted the direction of the TMS-evoked movement toward the practiced direction (Classen, Liepert, Wise, Hallett, & Cohen, 1998).

Sensorimotor planning has been shown to be affected by single-pulse TMS. When delivered over right, but not left, posterior parietal cortex (PPC), or over right or left dorsolateral prefrontal cortex, single-pulse TMS causes errors in the amplitude of contralateral memory-guided saccades (Müri et al., 2000; Müri, Vermersch, Rivaud, Gaymard, & Pierrot-Deseilligny, 1996; Oyachi & Ohtsuka, 1995). The timing of the TMS effect on saccade amplitude is much earlier for PPC than for dorsolateral prefrontal cortex, suggesting that PPC participates in the programming of saccade amplitude, and that the dorsolateral prefrontal cortex participates in sequence memorization. Single-pulse TMS of the PPC also disrupts eye-hand coordination (Van Donkelaar, Lee, & Drew, 2000). When subjects make an open-loop pointing response to a target that is accompanied by a large saccade, the pointing response is greater than when accompanied by a small saccade. TMS delivered 0–100 ms prior to the accompanying saccade disrupts the dependence of pointing amplitude on saccade amplitude. Pulses delivered earlier or later than this time window have little effect on the PPC's integration of saccade amplitude information into planning the pointing response.

TMS has also shown the importance of the PPC in adjusting to sudden visual target displacements during limb movements (Desmurget et al., 1999). A saccadic eye movement precedes the onset of open-loop pointing to a visual target. Finger movements start near the end of the saccade. If the visual target is displaced during the saccade, then the new target location is recomputed at the end of the saccade and this visual information is used to adjust ongoing finger movement trajectory. However, if TMS is delivered to the PPC near the end of the saccade, then the adjustment in finger movement trajectory is attenuated. The PPC may thus be critical in estimating ongoing hand location, computing motor error in a planned movement, and transmitting signals to adjust motor trajectories.

The roles of parietal and prefrontal areas in attention have also been studied using single-pulse TMS. TMS delivered over right parietal cortex increases reaction time during a conjunction search task but not during a popout detection task, suggesting right parietal cortex's role in search tasks requiring attention (Ashbridge, Walsh, & Cowey, 1997; Walsh, Ashbridge, & Cowey, 1998, 1999). Although single-pulse TMS disrupts attention to the task, this disruption is not significant enough to affect accuracy. In a different paradigm, single-pulse TMS delivered over right parietal cortex during a line bisection task causes subjects to overcome a bias to report the left side of the line as being longer than the right, a phenomenon called pseudoneglect (Fierro et al., 2000). This effect was not seen when TMS was delivered over left parietal cortex.

3. Paired-pulse and double-coil TMS

TMS can be delivered as a pair of pulses through a single coil or as simultaneous double pulses through two coils placed in different brain locations (Table 1).

The paired-pulse technique, using a subthreshold conditioning pulse followed by a suprathreshold test stimulus delivered through a single coil, has been used to study intracortical inhibition and facilitation (Chen et al., 1998; Kujirai et al., 1993). When delivered to motor cortex with an interstimulus interval of 1–4 ms, the conditioning pulse suppresses the amplitude of the motor potential evoked by the test pulse, consistent with intracortical inhibition. With interstimulus intervals of 8–15 ms, the test pulse evokes a larger motor potential than an equivalent single-pulse TMS, consistent with intracortical facilitation.

This paired-pulse technique has been used to study intracortical inhibition and facilitation in upper and lower extremity muscles, both distal and proximal. The inhibitory and facilitory effects appear to operate via separate mechanisms and exhibit variable neuroplasticity dependent on the type of motor task that is practiced or learned (Chen et al., 1998; Liepert, Classen, Cohen, & Hallett, 1998). A similar pattern of intracortical inhibition and facilitation has also been described with paired-pulse studies of parietal cortex using the task of discriminating a tactile electrical stimulus (Oliveri et al., 2000).

Paired pulses of TMS delivered unilaterally through the same coil to the frontal eye fields shorten the latency of contralateral, but not ipsilateral, memory-guided saccades. This facilitation occurs with a 50 ms interval between pulses, but not with much shorter or longer inter-pulse intervals (Wipfli et al., 2001).

Delivering one pulse of TMS to the motor cortex in one hemisphere suppresses the amplitude of motor potentials evoked in hand muscles by a second pulse delivered 6–30 ms later over the opposite homotopic hemisphere. This inhibitory event is thought to be mediated via transcallosal inhibition (Di Lazzaro et al., 1999; Ferbert et al., 1992). Similarly, delivering one pulse of TMS through a coil placed over the cerebellum suppresses the size of a hand motor potential evoked by a second pulse delivered 5–7 ms later to motor cortex. This effect may be mediated via cerebellar inhibition of motor cortex (Ugawa, Uesaka, Terao, Hanajima, & Kanazawa, 1995).

Double-pulse TMS delivered simultaneously through two coils has been used for comparing the processing times of different brain regions and for studying intracortical interactions. TMS delivered simultaneously through two coils placed bilaterally over the temporo-parieto-occipital junction (TPO) perturbs the perception of motion stimuli 20 ms later than bilateral TMS of occipital cortex, consistent with feedforward visual processing (Anand, Olson, & Hotson, 1998). Although bilateral TMS of TPO does not always selectively disrupt motion discrimination tasks, it has a weaker effect on color discrimination. If single-pulse TMS is delivered to TPO, moving phosphenes may be elicited, rather than the stationary phosphenes evoked from occipital cortex (Pascual-Leone & Walsh, 2001). However, if TMS is delivered first to TPO through one coil followed by a second subthreshold pulse delivered 5–45 ms later to occipital cortex, the moving phosphene percept is attenuated. This finding is consistent with fast backward connections from motion vision areas to primary visual areas that may be essential for visual awareness.

TMS delivered bilaterally through two coils over temporal cortex selectively increases reaction time in a visual-object working memory task (Oliveri et al., 2001). On the other hand, bilateral TMS of parietal cortex selectively increases reaction time in a visual-spatial working memory task. Bilateral TMS of dorsolateral prefrontal cortex increases reaction times in both types of working memory tasks, but the effect occurs later than the temporal and parietal TMS effects. Accuracy in these working memory tasks is not affected by bilateral TMS to any of the regions studied. Finally, the accuracy of discriminating between words and non-words is not altered by bilateral TMS delivered to the posterior temporo-parietal cortex (Cortez et al., unpublished results).

4. Repetitive TMS

In rTMS protocols, a train of magnetic pulses is delivered for many milliseconds to several seconds at a frequency of 1–25 Hz. The pulses' effects temporally summate to cause a greater change in neural activity than a single pulse, often enabling the researcher to study functions that are not affected by single-pulse TMS. The disadvantage of using rTMS is that it can pose a safety risk to the subject, which will be discussed in the last section of the paper. Table 2 summarizes the neurophysiological uses of rTMS.

4.1. Motor cortex and systems

While single-pulse TMS delivered over the frontal eye fields (FEF) does not evoke saccadic eye movements, rTMS elicits saccades when delivered during a double-step saccade task in some subjects (Li et al., 1997). rTMS must be delivered during the preparatory period of a saccade to a remembered target location following extinction of a stationary fixation target. In this condition rTMS evokes small, multi-step saccades that are time-locked to the repetitive pulses. The evoked saccades are in the direction of the intended saccade regardless of whether the direction is contralateral or ipsilateral to the stimulated FEF. rTMS delivered over the FEF increases rCBF in that region (Paus et al., 1997). rTMS over the right FEF also delays the onset of the first saccade used in reading an array of words, but otherwise does not alter the rate of reading saccades (Leff, Scott, Rothwell, & Wise, 2001). In contrast, rTMS of the left PPC slows the rate of all reading saccades. The right FEF may be important in the preparation of the first saccade when reading a new line of text, while the left PPC is more critical for maintaining a sequence of reading saccades across the line of text.

Repetitive TMS can also modulate the excitability of corticospinal output motoneurons. When delivered at 1 Hz to primary motor or premotor cortex, rTMS decreases motor potential amplitude for several minutes following stimulation

Table 2
Investigative uses of rTMS

Motor systems
Increases and decreases motor cortex excitability
Increases the duration of the silent period
Disrupts complex volitional movements
Evokes small multi-stepped saccades
Delays saccade initiation
Visual systems
Prolongs occipital cortex processing time
Contralateral visual extinction
Decreases occipital cortex excitability
Somatosensory systems
Elicits sensory paresthesia
Disrupts tactile sensation
Sensorimotor integration and cognition
Disrupts picture naming
Disrupts speech
Disrupts working memory and other forms of memory
Facilitates analogic reasoning
Slows speed of saccade initiation in reading
Modulates attentional processing
Emotion
Modulates happiness and sadness
Alters processing of emotional facial expressions

(Chen et al., 1997a; Gerschlager et al., 2001; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Muellbacher, Ziemann, Boroojerdi, & Hallett, 2000; Wassermann et al., 1996c). This effect is even seen transcallosally (Wassermann, Wedegaertner, Ziemann, George, & Chen, 1998). Conversely, rTMS delivered at 5–20 Hz can excite primary motor cortex, as evidenced by an increased motor potential amplitude (Berardelli et al., 1998; Chen, 2000; Jennum, Winkel, & Fuglsang-Frederiksen, 1995; Maeda et al., 2000; Pascual-Leone, Valls-Solé, Wassermann, & Hallett, 1994b; Wu, Sommer, Tergau, & Paulus, 2000).

Also demonstrating an inhibitory effect, rTMS delivered over primary motor cortex at frequencies greater than 3 Hz can prolong the silent period following the evoked movement without changing the amplitude of the motor evoked potential (Berardelli et al., 1999; Romeo et al., 2000). Finally, rTMS delivered to primary or supplementary motor cortex can disrupt complex finger movements (Chen, Cohen, & Hallett, 1997b, 1997d; Gerloff, Corwell, Chen, Hallett, & Cohen, 1997, 1998).

4.2. Visual cortex and sensory systems

A few studies have used rTMS to study the visual system. Amassian et al. (1993) found that double pulse and rTMS delivered shortly after the offset of a visual display could delay the processing of visual information in visual cortex. rTMS delivered unilaterally over occipital cortex impairs detection of stimuli in the contralateral visual field, while rTMS of parietal cortex impairs detection of stimuli in the contralateral visual field only during simultaneous presentation of stimuli in contralateral and ipsilateral visual fields (Pascual-Leone et al., 1994b). The effect on parietal cortex is consistent with visual extinction. rTMS delivered at 1 Hz to occipital cortex for 15 min increases the threshold for eliciting phosphenes, consistent with a decrease in occipital cortex excitability. The decreased excitability lasts at least 10 min and does not spread to alter motor cortex excitability (Boroojerdi, Prager, Muellbacher, & Cohen, 2000b).

Interestingly, rTMS delivered over the occipital cortex of blind subjects degrades tactile sensation and the ability to read Braille and embossed Roman letters (Cohen et al., 1997). Because these subjects became blind at an early age, this result points to plasticity in brain organization during development.

Stimulating the postcentral gyrus with rTMS can elicit paraesthesia in a somatotopic manner (Sugishita & Takayama, 1993). Stimulating primary motor cortex can also cause paraesthesia in the fingers (Jahanshahi et al., 1997).

4.3. Higher cognitive processing

rTMS has been used to study the neural basis of language, working memory, sensorimotor processing, attention, and emotion. rTMS delivered over frontal or temporal cortex can disrupt picture naming (Wassermann et al., 1996a, 1999) and picture-word verification (Flitman et al., 1998), but has also been shown to decrease the latency for picture naming (Sparing et al., 2001; Wassermann et al., 1999).

Several laboratories have examined the use of rTMS as a non-invasive method for determining hemispheric language dominance, with inconsistent results (Claus et al., 1993; Epstein et al., 1996, 1999, 2000; Jennum, Friberg, Fuglsang-Frederiksen, & Dam, 1994a; Michelucci et al., 1994; Pascual-Leone, Gates, & Dhuna, 1991). rTMS delivered to either hemisphere lateral to the optimal location for evoking a hand movement disrupts speech in association with activation of facial muscles. Subjects feel that they cannot control their facial muscles; this form of speech disruption may therefore be attributed to the effect of rTMS on muscles innervating oral and jaw muscles. rTMS delivered more anteriorly over the middle and inferior frontal gyri also disrupts speech, but the effect is predominantly seen for stimulation of the

dominant language hemisphere. There is no activation of facial muscles and subjects feel that they are unable "to get the words out" (Stewart, Walsh, & Rothwell, 2001b). Speech disruption with rTMS of left middle and inferior frontal cortex occurs in most but not all normal subjects. Unfortunately, some subjects withdraw from such studies because the stimulation is too uncomfortable.

rTMS used in conjunction with functional brain imaging has been instrumental in demonstrating involvement of the dorsolateral prefrontal cortex in working memory and long-term episodic memory (Grafman et al., 1994; Mottaghy et al., 2000; Pascual-Leone & Hallett, 1994; Rossi et al., 2001). A hemispheric asymmetry may exist in encoding and retrieval of episodic memory, with the right prefrontal cortex specialized for retrieval during recognition tasks and the left prefrontal cortex more crucial than the right for encoding pictorial memory traces. rTMS of dorsolateral cortex also causes errors in the amplitude and direction of memory-guided saccades when delivered during the working memory phase of this delayed response task. In contrast, rTMS of the posterior parietal cortex disrupt memory-guided saccades when delivered early during the "sensory" phase of the task, but not later during the working memory phase (Brandt, Ploner, Meyer, Leistner, & Villringer, 1998). rTMS studies of dorsolateral prefrontal cortex have also shown its contribution to sequential learning guided by spatial cues (Robertson, Tormos, Maeda, & Pascual-Leone, 2001), and left prefrontal cortex facilitation of analogic reasoning (Boroojerdi et al., 2001). Investigations of the role of parietal cortex in spatial working memory have given variable results (Hong, Lee, Kim, Kim, & Nam, 2000; Hufnagel, Claus, Brunhoelzl, & Sudhop, 1993; Kessels, d'Alfonso, Postma, & de Haan, 2000).

Researchers have used rTMS to confirm the importance of parietal and frontal cortex in attention. Attention to a visual task is improved by low frequency rTMS delivered over the ipsilateral parietal lobe prior to task execution (Hilgetag, Theoret, & Pascual-Leone, 2001). Conversely, rTMS delivered to the contralateral parietal lobe disrupts attention in the same task. rTMS delivered over dorsolateral prefrontal cortex can modulate performance in a response selection task that requires high attentional resources (Hadland, Rushworth, Passingham, Jahanshahi, & Rothwell, 2001; Jahanshahi et al., 1998), and activates dorsolateral prefrontal cortex as measured by PET (Jahanshahi, Dirnberger, Fuller, & Frith, 2000). In frontal and central cortex, rTMS delays electrical activity related to auditory attention (Jing et al., 2001).

4.4. Emotion

rTMS can affect mood in a lateralized fashion. In normal subjects, rTMS delivered over left prefrontal cortex increases self-ratings of sadness and decreases self-ratings of happiness, while rTMS of right prefrontal cortex decreases sadness self-ratings (George et al., 1996; Pascual-Leone, Catala, & Pascual-Leone, 1996). rTMS delivered over the medial-frontal cortex impairs the processing of angry facial expressions but not happy facial expressions (Harmer, Thilo, Rothwell, & Goodwin, 2001). There are a few potential mechanisms by which rTMS may affect mood. It may produce neuroendocrine effects similar to antidepressants in rats (Keck et al., 2001), may stimulate striatal dopamine release (Strafella, Paus, Barrett, & Dagher, 2001), may modulate neurotransmitter and neuromodulator release (Keck et al., 2000), and may increase cerebral blood flow in stimulated regions and those connected to them (Speer et al., 2000).

5. Control conditions

TMS not only induces electrical current in the brain but also has ancillary effects, such as a loud auditory click with pulse delivery, somatosensory stimulation of the

scalp, direct motor stimulation of scalp, face and neck muscles, and eyelid blinking. All of these effects can startle subjects or distract them from the task they are to perform. Thus, it is important to verify that the results obtained during TMS trials are truly due to neurophysiological interaction with a region subserving the function being tested instead of due to the ancillary or non-specific effects. Adequate anatomical, task, or timing controls strengthen the conclusions that can be drawn from TMS studies.

Anatomic controls are used to demonstrate that TMS results are location-specific. Topographic mapping of motor cortex, visual scotoma, or phosphenes is an established anatomic control method. Results can also be compared with results obtained with coils placed over other cortical areas. These controls are not completely satisfactory, however, because moving the coil to different locations can change the ancillary effects. For example, stimulating over occipital cortex produces little motor response compared to stimulating frontal cortex. Even as one moves more laterally over frontal cortex, additional scalp and cranial nerves may be activated and interfere with task performance.

Task controls have also been used. For example, TMS studies of motion processing in extrastriate cortex have shown selective impairment of motion discrimination when compared to a stationary spatial acuity task (Beckers & Zeki, 1995; Hotson, Braun, Herzberg, & Boman, 1994). Difficulties in matching visual stimulus size, duration, and luminance, and task difficulty introduce limitations with these types of task controls.

Timing controls offer a superior method for TMS studies. Task, coil location, and TMS intensity are kept constant while TMS is delivered at different delays relative to task onset. If a TMS effect is only observed in a discrete time window, then the results appear convincing. This technique, introduced by Amassian's laboratory, is particularly effective in demonstrating TMS effects with sensory, especially visual, processing and sensorimotor processing (Amassian et al., 1989). The technique has limitations, however. For example, if one delivers TMS during the presentation of a visual display, there is commonly an accompanying eyelid blink that interferes with vision and may influence results. To avoid the blink during visual tasks, one can deliver TMS in a time window that begins after the end of a brief visual display. A means to control for a blink artifact is to determine the effect of blinking on task performance by stimulating the seventh cranial nerve at a peripheral site.

Sham controls have also been implemented either by altering coil orientation so that much of the coil does not touch the skull, or by using a sham coil that simulates the magnetic coil without delivering a magnetic pulse to the brain.

Earplugs not only protect hearing, but can also decrease the perceived amplitude and therefore the distractive effect of the auditory click. As subjects become accustomed to TMS, they report that the ancillary auditory, somatosensory, and motor stimulation are less distracting.

6. Safety of TMS research

TMS is believed to only cause a transient change in neural activity without long-lasting effects. The possibility of unforeseen risks in the long term, however, cannot be completely excluded.

As in any study of human subjects, informed consent is obtained from subjects prior to participating in TMS studies. The consent form states the known risks of TMS and the possibility that there may be unforeseen risks in the long term that are currently unknown. The consent form includes questions that screen control subjects for various conditions that may increase the risk of adverse effects (Table 3). The Brain Stimulation Unit at the National Institute of Neurological Disorders and

Table 3
Conditions that may increase the risk of adverse effects of transcranial magnetic stimulation

Pregnancy (effects on pregnant women are unknown)	Personal or family history of seizures, including febrile seizures as an infant
Metal implants in the head	Previous brain neurosurgery
Cardiac pacemakers	Unstable major medical conditions
Poorly-controlled migraine headaches	Medications that lower seizure threshold
History of major head injury	Neurological disorders
History of stroke	Major psychiatric disorders

Stroke has prepared a safety questionnaire that identifies potential safety problems related to TMS (Keel, Smith, & Wassermann, 2001).

6.1. Safety of single-pulse TMS

TMS safety studies in human subjects have been concerned with the theoretical possibility of electrical injury to the brain, brain changes manifested in an altered electroencephalogram (EEG) or hormonal aberrations, disruption in cardiovascular stability, and persistent changes in cognitive, perceptual, or motor function. Single-pulse TMS in healthy adults appears to carry little risk beyond occasionally causing local discomfort at the site of stimulation or a transient headache in susceptible subjects. No short- or long-term sequelae have been described in safety studies in presumed normal adult subjects (Bridgers, 1991; Bridgers & Delaney, 1989; Chokroverty et al., 1995; Ferbert, Mussmann, Menne, Buchner, & Hartje, 1991; Krain, Kimura, Yamada, Cadwell, & Sakamaki, 1990; Levy, Oro, Tucker, & Haghighi, 1990). In a comprehensive safety study of suprathreshold single-pulse TMS, Chokroverty et al. (1995) found no change in blood pressure, heart rate, EEG, serum prolactin level, serum cortisol level, or in a variety of memory, cognitive, learning, sensory, and motor tests. In fact, two cognitive tests showed improvement immediately after the TMS sessions. EEG and the battery of psychometric tests showed no change 16–24 months after the study. Bridgers and Delaney (1989) tested similar functions, and found no change in EEG, a decrease in serum prolactin levels, and no change in cognitive and motor tests, except for an improvement in oral word association.

A study in which three monkeys received 7000 maximum intensity single pulses delivered in daily increments over thirty days demonstrated no short- or long-term deficits in higher cerebral function or other adverse effects (Yamada, Tamaki, Wakano, Mikamia, & Transfeldt, 1995). Another study suggested that the auditory click caused by a pulse of transcranial magnetic stimulation may raise the hearing threshold in rabbits (Counter, Borg, Lofqvist, & Brismar, 1990), but studies in humans have found no evidence of lasting hearing loss due to TMS (Pascual-Leone et al., 1992). As a precaution, some laboratories have subjects wear earplugs during TMS sessions.

Safety studies of single-pulse TMS in patients with neurological disorders have demonstrated no permanent sequelae, but have raised a concern about a rare possibility of activating a seizure. In patients with intractable seizures, single-pulse TMS can activate a seizure focus and even rarely precipitate an epileptic seizure (Classen et al., 1995; Hufnagel & Elger, 1991; Hufnagel, Elger, Durwen, Boker, & Entzian, 1990a, 1990b; Schuler, Claus, & Stefan, 1993; Tassinari et al., 1990). But even in these medically intractable epileptic patients, "no adverse effects were noticed by either the patients or the investigator" (Hufnagel et al., 1990a), and seizure activation is difficult. Individuals with stroke or other brain disorders may have a lower threshold for seizure activation, and several such patients have been reported to have seizures shortly after TMS (Homberg & Netz, 1989; Wassermann, 1998).

The safety of single-pulse TMS delivered over the surface of the cerebellum has not been studied as extensively as the safety of TMS delivered to the cerebral cortex. No adverse consequences, however, have been reported for TMS of the cerebellum in normal subjects or neurological patients (Amassian, Cracco, Maccabee, & Cracco, 1992; Gironell, Kulisevksy, Lorenzo, Barbanoj, & Pascual, 2000; Hashimoto & Ohtsuka, 1995; Meyer, Roricht, & Machetanz, 1994; Nezu, Kimura, Takeshita, Osaka, & Tanaka, 1998; Saito, Yokota, & Yuasa, 1995; Ugawa, Uesaka, Terao, Hanajima, & Kanazawa, 1994, 1995; Ugawa et al. 1997a; Ugawa, Uesaka, Terao, Hanajima, & Kanazawa, 1997b, 1996; Werhahn, Taylor, Ridding, Meyer, & Rothwell, 1996; Zangemeister & Nagel, 2001).

6.2. Safety of paired-pulse and double-coil TMS

We are not aware of any safety studies that specifically address paired-pulse or double-coil TMS. It is typically assumed that the associated risk is greater than that posed by single-pulse TMS and substantially less than that posed by rTMS.

6.3. Safety of rTMS

rTMS is a powerful technique for neurophysiological study with no known adverse long-term effects in normal human subjects. Studies of the anatomical effects of rTMS have shown that conventional and diffusion-weighted magnetic resonance imaging are normal following long duration, high-intensity rTMS that exceeded safety guidelines (Niehaus, Hoffmann, Grosse, Roricht, & Meyer, 2000), and MRI is normal following rTMS used for 2 weeks in treating depression (Nahas et al., 2000). Moreover, no pathological changes are seen in resected temporal lobe tissue following approximately 2000 rTMS pulses (Gates, Dhuna, & Pascual-Leone, 1992).

Most safety studies have not reported adverse long-term effects or sustained changes in cognitive function in subjects receiving rTMS (Flitman et al., 1998; Hufnagel et al., 1993; Jennum et al., 1995; Padberg et al., 1999; Speer et al., 2000; Valzania et al., 1994; Wassermann, 1998). One study found degradation in short-term verbal memory immediately following rTMS, but the effect did not persist following the study and was attributed to the short inter-train intervals that were also found to cause seizures in normal subjects (Flitman et al., 1998). Performance on standard neuropsychological tests is not adversely affected by rTMS sessions; instead, verbal memory tends to improve and motor reaction time tends to decrease (Jahanshahi et al., 1997; Loo et al., 2001; Padberg et al., 1999; Pascual-Leone et al., 1993; Wassermann et al., 1996c).

The endocrine system has been another focus of safety studies. While Pascual-Leone et al. did not find that rTMS affected hormonal levels in humans, Wassermann et al. detected a decrease in serum prolactin levels following rTMS, which is opposite the effect seen after a seizure (Pascual-Leone et al., 1993; Wassermann et al., 1996c). George et al. (1996) found that an improved mood resulting from rTMS was accompanied by an increase in thyroid-stimulating hormone level.

rTMS does have the potential for short-term adverse side effects and risks. Subjects may report discomfort due to stimulation of scalp, facial, neck, or shoulder muscles, which depends on coil location and stimulation parameters. Temperature of the rTMS coil needs to be monitored so that it does not overheat to cause additional scalp discomfort. Headaches that respond to mild analgesia may occur and subjects with a history of severe migraine headaches may develop a migraine headache following rTMS (Wassermann, 1998). Studies of language localization using rTMS have reported additional side effects such as crying due to inability to speak, dysarthria, and pain (Michelucci et al., 1994; Pascual-Leone et al., 1991). In response, stimulation parameters have been identified that improve subjects' comfort while

allowing language hemispheric dominance to be effectively studied (Epstein et al., 1996).

The short-term risk of greatest concern with rTMS is the induction of seizures. The neurophysiological excitability induced by even focal rTMS can spread beyond the site of stimulation. rTMS can activate seizures in epileptic patients, though seizures do not occur in all patients and they are often difficult to elicit (Chen et al., 1997c; Dhuna, Gates, & Pascual-Leone, 1991; Flitman et al., 1998; Jennum, Winkel, Fuglsang-Frederiksen, & Dam, 1994b; Schulze-Bonhage, Scheufler, Zentner, & Elger, 1999; Wassermann, 1998; Wassermann, Cohen, Flitman, Chen, & Hallett, 1996b).

Even in normal healthy subjects, prolonged, high intensity, rTMS with rates of 10–25 Hz can produce partial seizures with or without secondary generalization. For this reason, the intensity, rate, and duration of rTMS delivered to a subject follow established safety guidelines that have been recently revised (Chen et al., 1997c; Wassermann, 1998).

Wassermann (1998) provided a comprehensive report of new guidelines based on the deliberations of an ''International Workshop on the Safety of Repetitive Transcranial, Magnetic Stimulation, June 5–7, 1996.'' He reiterated three requirements central to research on human subjects, namely, the need for informed consent, the requirement that the potential benefit of the research outweighs the risk as independently assessed by an investigational review board, and the need ''for equal distributions of the burdens and benefits of the research.'' The research should not be conducted on categories of vulnerable patients or subjects who are likely to bear the burden of the research without the potential for benefit.

Wassermann suggested three types of studies appropriate for rTMS. First are studies where there are reasons to expect direct benefit to patients, such as the treatment of major depression. Second are studies of the pathophysiology of a brain disorder that may add information leading to new therapeutic strategies. These studies would include the participation of normal subjects as controls. Third are studies in normal subjects or patients that are expected to produce original and important observations about brain function that cannot be obtained by safer methods. ''Normal subjects should be permitted to participate in rTMS research when it is likely to produce data that are of outstanding scientific and clinical value.''

Wassermann's report also recommended that rTMS studies follow established stimulation parameters, that studies include physiological and neuropsychological monitoring, that the rTMS laboratory be prepared for the acute medical management of seizures including appropriate life support equipment, and that there is support for the psychosocial consequence of having a seizure. His report also states that the absolute contraindications for rTMS include metal in the head (except for the mouth), intracardiac lines, and patients with increased intracranial pressure. Relative contraindications to rTMS include ''pregnancy, childhood, heart disease, cardiac pacemakers, medication pumps, tricyclic antidepressants, neuroleptics, and family history of epilepsy.''

Subsequent to Wassermann's 1998 report, Boylan, Pullman, Lisanby, Spicknall, and Sackeim (2001) published a study addressing the therapeutic effect of rTMS in Parkinson's disease. They delivered rTMS over supplementary motor cortex in eight patients. rTMS was delivered at a rate of 10 Hz, with an intensity of 110% of the patient's motor cortex threshold for 5-s trains of pulses. Forty of these 5-s trains of high-intensity, high-speed TMS were given over 40 min for a total of 2000 pulses per session. There was no therapeutic benefit, but rather a significant decrease in motor performance of the Parkinson's patients following rTMS. There was a trend for this decrement in motor performance to persist for a week. This study raised a concern that some neurological disorders render patients vulnerable to ''subtle but persistent adverse effects'' from long-duration, high-intensity, and high-speed TMS.

7. Conclusions

TMS provides a powerful investigative strategy for transiently and non-invasively activating or disrupting neurophysiological functions in human subjects. Current information indicates that single-pulse and paired-pulse/double-coil TMS are safe for studying normal human subjects. rTMS can pose a safety risk in normal subjects and safety guidelines have therefore been established.

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