Neuron
Primer

Transcranial Magnetic Stimulation: A Primer

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DOI 10.1016/j.neuron.2007.06.026

Transcranial magnetic stimulation (TMS) is a technique for noninvasive stimulation of the human brain. Stimulation is produced by generating a brief, high-intensity magnetic field by passing a brief electric current through a magnetic coil. The field can excite or inhibit a small area of brain below the coil. All parts of the brain just beneath the skull can be influenced, but most studies have been of the motor cortex where a focal muscle twitch can be produced, called the motor-evoked potential. The technique can be used to map brain function and explore the excitability of different regions. Brief interference has allowed mapping of many sensory, motor, and cognitive functions. TMS has some clinical utility, and, because it can influence brain function if delivered repetitively, it is being developed for various therapeutic purposes.

Principles of Magnetic Stimulation

Almost 30 years ago, Merton asked Morton to build a high-voltage electrical stimulator able to activate muscle directly rather than through the small nerve branches in the muscle. When built, he had the idea that this device could also stimulate the motor areas of the human brain through the intact scalp (transcranial electrical stimulation [TES]), and it worked (Merton and Morton, 1980). A brief, high-voltage electric shock over the primary motor cortex (M1) produced a brief, relatively synchronous muscle response, the motor-evoked potential (MEP). It was immediately clear that this would be useful for many different purposes, but a problem with TES is that it is painful. Five years later, Barker et al. (Barker et al., 1985) solved a number of technical problems and showed that it was possible to stimulate brain (as well as peripheral nerve) with magnetic stimulation (transcranial magnetic stimulation [TMS]), and this could be accomplished with little or no pain. TMS has now come into wide use, and TES is still used for selective purposes. TMS is most frequently used as a research tool to study brain physiology, but it has some clinical utility and is also being developed as a therapeutic tool.

For electrical stimulation between two electrodes placed on the scalp, current flows from anode to cathode. Near the scalp, the predominant direction of current flow is radial, but there are return loops that are tangential to the scalp. For magnetic stimulation, a brief, high-current pulse is produced in a coil of wire, called the magnetic coil (Figure 1). A magnetic field is produced with lines of flux passing perpendicularly to the plane of the coil, which ordinarily is placed tangential to the scalp. The magnetic field can reach up to about 2 Tesla and typically lasts for about 100 μs. An electric field is induced perpendicularly to the magnetic field. The voltage of the field itself may excite neurons, but likely more important are the induced currents. In a homogeneous medium, spatial change of the electric field will cause current to flow in loops parallel to the plane of the coil, which will be predominantly tangential in the brain. The loops with the strongest current will be near the circumference of the coil itself. The current loops become weak near the center of the coil, and there is no current at the center itself. Neuronal elements are activated by the induced electric field by two mechanisms. If the field is parallel to the neuronal element, then the field will be most effective where the intensity changes as a function of distance. If the field is not completely parallel, activation will occur at bends in the neural element.

Magnetic coils may have different shapes (Figure 2). Round coils are relatively powerful. Figure-of-eight-shaped coils are more focal, producing maximal current at the intersection of the two round components. A figure-of-eight-shaped coil with the two components at an angle, the cone-shaped coil, increases the power at the intersection. Another configuration is called the H-coil, with complex windings that permit a slower fall-off of the intensity of the magnetic field with depth (Zangen et al., 2005). In another design, the windings of a coil are around an iron core rather than air; this focuses the field and allows greater strength and depth of penetration (Epstein and Davey, 2002).

The results of TMS over M1 appear similar to those of TES. One difference, however, is that the latency of response is slightly shorter with TES, and explaining this difference opens the door to understanding the excitation mechanism of the two types of stimulation. It is likely that the mechanism of stimulation is similar in many parts of the brain, but we have detailed information only from M1, since the results can be measured in such detail. The difference in latency appears to be related to the nature of the descending volley in the corticospinal tract produced by the two types of stimulation (Figure 3) (Di Lazzaro et al., 1998). With TES, but typically not with TMS, there is an early D wave (direct wave) that reflects

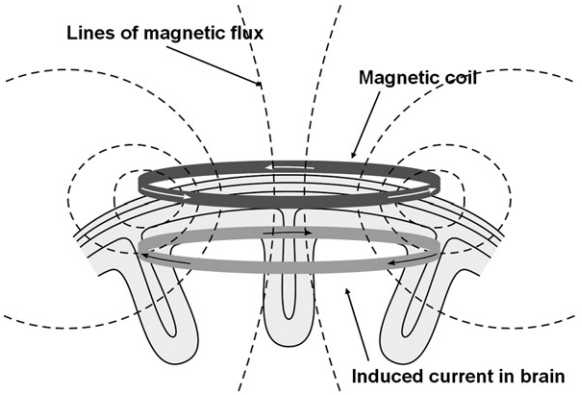

Figure 1. Illustration of Direction of Current Flows in a Magnetic Coil and the Induced Current in the Brain
From Hallett (2000), with permission.

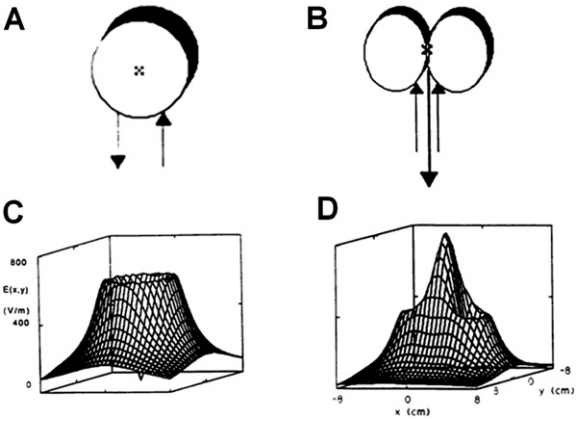

Figure 2. Magnetic Coil Shape Determines the Pattern of the Electric Field
Two magnetic coils with different shapes (A and B) and their resultant electric fields (C and D). Modified from Cohen et al. (1990), with permission.

direct activation of descending axons. With both types of stimulation, there is a series of later I waves (indirect waves) that reflect synaptic activation of the corticospinal neurons. The mechanism of I wave production is not completely clear. I waves come at intervals of about 1.5 ms and are either generated by increasingly long polysynaptic networks or recurrent synaptic networks. Comparing the responses from rotating the magnetic coil in different angles, the largest MEPs are produced when the current in the brain is directed in the posterior-anterior direction (optimally at an angle perpendicular to the central sulcus), and the first wave produced is typically the I1 wave (at about a 1.5 ms interval from the D wave). When brain current is lateral-medial, there can be a D wave produced first. When the brain current is anterior-posterior, the I3 wave (at about a 4.5 ms interval from the D wave) can be produced first. MEPs are also larger and earlier when the muscle is contracting at baseline as opposed to when it is at rest. This is largely due to the fact that the motor neuron pool is at a higher level of activity and it is easier to provoke an increase of activation.

Delivering a single pulse of TMS to the brain is very safe. Devices are now available that are capable of delivering high-frequency (1–50 Hz), repetitive TMS (rTMS). This can produce powerful effects that outlast the period of stimulation, inhibition with stimulation at about 1 Hz, and excitation with stimulation at 5 Hz and higher. rTMS, however, has the potential to cause seizures even in normal individuals. Safety guidelines describing limits for combinations of frequency, intensity, and train length have been developed, which should prevent most problems (Wassermann, 1998).

Corticomotor Conduction Time

One of the obvious measurements that can be made with TMS is central motor conduction time. This is the time from motor cortex to the motor neuron pool in the spinal cord or brainstem. It is calculated by taking the latency of the MEP and subtracting the peripheral conduction time. Peripheral conduction time may be obtained in two ways. The first is to stimulate over the spine that activates the nerve roots in the intravertebral foramina. This is slightly in error since it misses the segment from the spinal cord to the foraminal region. The second method is to use the F wave, using the formula (F wave latency + M wave latency − 1)/2. Upon stimulating a motor nerve, the M wave is the direct muscle response, and the F wave is the muscle response produced by activation of the alpha motoneuron by the antidromic volley. This is more accurate, but a bit more time consuming (and painful).

Activation, Inhibition, and Mapping

Using TMS, the brain can be briefly activated or briefly inhibited; in fact, likely both occur with each stimulus in differing amounts and with different time courses. This effect can be used to localize brain functions in both space and time. Applications were first in the motor system but have now been used to map sensory processes and cognitive function.

Mapping the motor cortex by moving the coil over the surface of the scalp and recording MEPs from different muscles has been fairly straightforward. MEP mapping is an example of mapping in space with activation. Different body parts, such as arm and leg, are completely separate, but there is overlapping of muscles in the same body part (Wassermann et al., 1992) (Figure 4). Such studies have also allowed the demonstration of weak ipsilateral pathways to upper extremity muscles as well as the more powerful contralateral ones. Mapping of cranial nerve muscles has also been done, revealing innervations that are bilateral, bilaterally asymmetric, and unilateral, and also allowed confirmation of the innervation of orbicularis oculi by the cingulate cortex (Sohn et al., 2004). The patterns of muscle activity provoked by TMS have some physiological relevance, as these can be recognized as principal components of natural movement (Gentner and Classen, 2006).

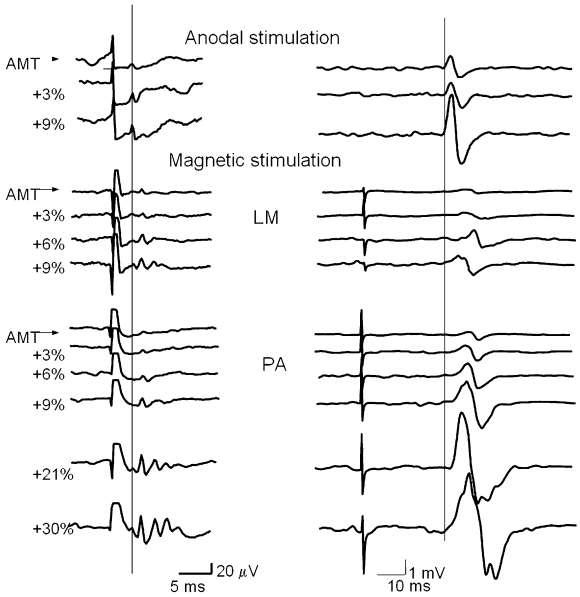

Figure 3. Descending Volleys Recorded from the Spinal Cord and the Resultant MEPs after Different Types of TES and TMS
Anodal stimulation is from TES, and TMS is delivered in both lateral-medial (LM) and posterior-anterior (PA) directions in various intensities. AMT is active motor threshold, and other intensities are at percentages above that. The vertical timeline for the descending volleys is at the D wave and, for the MEPs, at the onset of the MEP from TES. Note that a D wave is produced by anodal TES and that a small D wave is produced by LM TMS at low intensity of stimulation. For the PA stimulation, the I1 wave is first produced by low-intensity stimulation, and a D wave, as well as later I waves, is produced at higher stimulation intensity. From Rothwell (2004), as modified from Di Lazzaro et al. (1998), with permission.

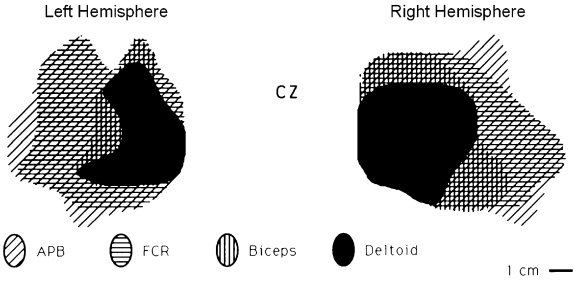

Figure 4. TMS Mapping of Upper Extremity Muscles in Right and Left Sides of One Normal Subject after Stimulation of the Contralateral M1s
From Wassermann et al. (1992), with permission.

While TMS of occipital cortex can produce phosphenes, it can also produce a transient scotoma. Scotoma mapping is an example of mapping in time with inhibition. In the first demonstration of this, subjects were shown briefly presented, randomly generated letters on a visual monitor, and TMS was delivered after the visual stimulus (Amassian et al., 1989). When delivered at an interval less than 40–60 ms or more than 120–140 ms, letters were correctly reported; but at intervals of 80–100 ms, a blur or nothing was seen. Presumably this indicates important visual processing during that time interval. Subsequent studies with more sensitive techniques indicate also an earlier period of suppression at about 30 ms, likely indicating the initial arrival of visual information to occipital cortex (Figure 5) (Corthout et al., 1999b). Additionally, TMS of V5 can selectively interfere with the perception of motion of a stimulus without impairing its recognition (Beckers and Zeki, 1995; Walsh et al., 1998). Such data provide support to the concept arising from imaging studies that V5 is the motion perception region of the brain.

Studies of vision have also revealed the importance of backprojections for perception. For example, there appears to be an important projection from V5 to V1. TMS over V5 can produce a moving phosphene, but when the V5 stimulus is followed by a TMS over V1 at an interval of 5–45 ms, the phosphene is degraded (Pascual-Leone and Walsh, 2001). Moreover, a similar backprojection exists from the frontal eye field (FEF) to V5. TMS over FEF impairs visual target discrimination (independent of its role in eye movements) (O'Shea et al., 2004) and, at an interval of 20–40 ms, can modify the phosphene threshold of TMS over V5 (Silvanto et al., 2006).

High-frequency rTMS, at about 5–10 Hz, has been used as a more powerful stimulus to produce a brief period of inhibition in space and time. One example in the motor system is the study of the role of the supplementary motor cortex (SMA; more exactly, the mesial frontocentral cortex) in the production of sequential finger movements (Gerloff et al., 1997). Stimulation over the SMA induced accuracy errors in complex, but not simple, sequences. Additionally, the errors occurred in subsequent elements of the sequence rather than those occurring at the time of the stimulation itself. The data support a critical role of the SMA in the organization of forthcoming movements in complex motor sequences.

When patients who are blind from early life read Braille, they activate their occipital cortex, as demonstrated by functional neuroimaging (Sadato et al., 1996). This is a striking example of transmodal plasticity, where somatosensory information gets routed to the visual cortex. The observation from neuroimaging alone, however, did not prove that the activity in visual cortex was being used for actual useful analysis of the information. Using rTMS during the reading showed that function was impaired when the visual cortex was disrupted (Cohen et al., 1997). Hence, TMS showed that the occipital activity was a necessary component of the processing. In a similar situation, studies with fMRI showed that the ventral premotor cortex was activated with counting of large numbers, but not small ones (up to 4) (Kansaku et al., 2007). Correlative studies with rTMS showed that disruption of the ventral premotor cortex interfered with this counting behavior, showing that this region appears to be necessary for it.

TMS has helped localize memory processes. For example, several studies give evidence for a role of the left dorsolateral prefrontal cortex (DLPFC) in working memory.

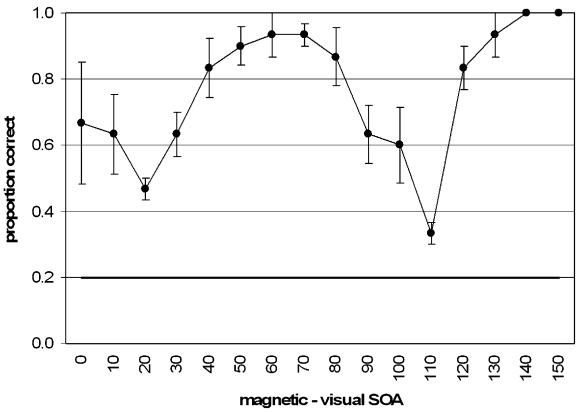

Figure 5. Mapping Visual Processing in Time
The x axis shows magnetic-visual stimulus onset asynchrony (SOA), i.e., time of onset of the magnetic stimulus minus time of onset of the visual stimulus (positive values thus indicate that the magnetic stimulus came after the visual stimulus). The y axis shows proportion of letters correctly identified as a function of magnetic-visual SOA, averaged across three subjects who showed the first visual dip. Error bars denote ± 1 SEM. The thick horizontal line indicates that chance level was 20%. Modified from Corthout et al. (1999a), with permission.

Single-pulse TMS between presentations of letters impaired ability to match letters on a three-back task (Mull and Seyal, 2001). Low-frequency rTMS over the left DLPFC interfered with short-term memory for words, but not for faces (Skrdlantova et al., 2005). Double-pulse TMS over DLPFC at 100 ms interval interfered with working memory for words after a reading task (Osaka et al., 2007). Consolidation of a simple motor skill, phasic pinch force, was disrupted by stimulation selectively over M1, without disruption of other aspects of motor function (Muellbacher et al., 2002). Another study confirmed this finding, but failed to find a similar disruption of learning of movement dynamics in a force field, suggesting that only some types of motor consolidation occur in M1 (Baraduc et al., 2004). On the other hand, rTMS of M1 prior to learning of movement dynamics did interfere with consolidation without interfering with the learning itself (Richardson et al., 2006).

There are numerous examples of how this technique has helped localize a wide variety of other cognitive functions; a few other findings are noted here. Low-frequency rTMS over either the right or left prefrontal cortex (but not the parieto-occipital cortex) impaired behavior on a task involving visuo-spatial planning (Basso et al., 2006). Disruption of the right (but not left) dorsolateral prefrontal cortex reduced a subject's willingness to reject an unfair offer, even though they still could appreciate the offer as unfair (Knoch et al., 2006). Selective stimulation over Wernicke's area improves cognitive function by shortening the latency for picture naming (Mottaghy et al., 2006).

Assessment of Cortical Excitability

Various TMS measures of the motor cortex can evaluate different aspects of cortical excitability. Such measures are useful in understanding changes in brain physiology seen, for example, in the setting of cortical plasticity and brain disorders. Some of the common measures are listed here.

Threshold

The threshold for producing an MEP reflects the excitability of a central core of neurons that arises from the excitability of individual neurons and their local density. Since it can be influenced by drugs that affect Na and Ca channels, it must indicate membrane excitability (Ziemann, 2004). Because the MEP is small, the threshold measure (with posterior-anterior brain current flow) reflects the influence of mainly the I1 wave.

Recruitment Curve

The recruitment curve is the growth of MEP size as a function of stimulus intensity and background contraction force. This measurement is less well understood but must involve neurons in addition to the core region activated at threshold. These neurons have higher threshold for activation, either because they are intrinsically less excitable or they are spatially further from the center of activation by the magnetic stimulus. These neurons would be part of the "subliminal fringe" and will contribute to I2 and later I waves.

Short Intracortical Inhibition and Facilitation

Short intracortical inhibition (SICI) and facilitation (ICF) are obtained with paired-pulse studies and reflect interneuron influences in the cortex.(Ziemann et al., 1996) In such studies, an initial conditioning stimulus is given—enough to activate cortical neurons, but small enough so that no descending influence on the spinal cord can be detected and there is no MEP. A second test stimulus, at suprathreshold level, follows at a short interval. Intracortical influences initiated by the conditioning stimulus modulate the amplitude of the MEP produced by the test stimulus. At very short intervals, less than 5 ms, there is inhibition, and at intervals between 8 and 30 ms, there is facilitation (Figure 6). SICI is likely largely a GABAergic effect, specifically GABA-A (Di Lazzaro et al., 2000a).

Silent Period

The silent period (SP) is a pause in ongoing voluntary EMG activity produced by TMS. While the first part of the SP is due in part to spinal cord refractoriness, the latter part is entirely due to cortical inhibition. This type of inhibition seems to be mediated by GABA-B receptors (Werhahn et al., 1999). SICI and the SP clearly reflect different aspects of cortical inhibition.

Long Intracortical Inhibition

Long intracortical inhibition (LICI) is assessed with paired suprathreshold TMS pulses at intervals from 50 to 200 ms. LICI and SICI differ, as demonstrated by the facts that with increasing test pulse strength, LICI decreases but SICI tends to increase, and that there is no correlation between the degree of SICI and LICI in different individuals (Sanger et al., 2001). Interestingly, LICI appears to inhibit SICI and shows some interaction of inhibitory mechanisms within the human motor cortex (Sanger et al., 2001). The mechanisms of LICI and the SP may be similar.

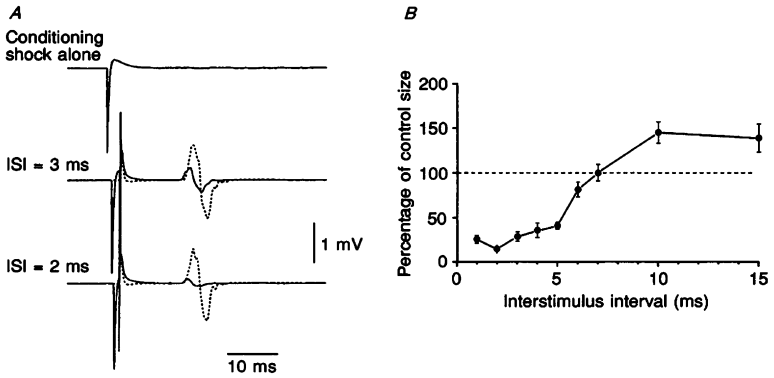

Figure 6. Technique of Producing Short Intracortical Inhibition and Intracortical Facilitation

Paired magnetic pulses are given. In (A), from top down: conditioning pulse alone, conditioning and test pulse at 3 ms interval, conditioning and test pulse at 2 ms interval. The MEP from the test pulse without the conditioning pulse is indicated in the second and third traces with dotted lines. This shows that the conditioning pulse, although not producing an MEP itself, can lead to inhibition of the test pulse. (B) illustrates the average effect on MEPs with paired pulses at different intervals. Error bars denote ± 1 SEM. There is inhibition at 1–5 ms interval and facilitation at 10 and 15 ms interval. From Kujirai et al. (1993), with permission.

Short and Long Afferent Inhibition

Short and long afferent inhibition (SAI and LAI) are produced at latencies of about 20 ms and 200 ms, respectively, after somatosensory stimulation of the hand (Di Lazzaro et al., 2000b). SAI has been demonstrated to be mainly muscarinic by its selective blockage by scopolamine.

Transcallosal Inhibition

Transcallosal inhibition (TCI) is the inhibition produced in the primary motor cortex in one hemisphere by stimulation of the opposite primary motor cortex. Inhibition occurs at intervals of 8–50 ms (Ferbert et al., 1992).

Premotor Cortex Inhibition

Premotor cortex inhibition is produced by stimulation of the premotor cortex either in the same or opposite hemisphere (Civardi et al., 2001; Mochizuki et al., 2004).

Plasticity

TMS can be used in a variety of ways to induce plastic changes in the brain, and this can be utilized to assess the capability for plasticity (Table 1). Additionally, induced plastic changes can be exploited therapeutically, and this aspect will be discussed below. An effective way to modulate synaptic efficacy is to activate a cell with two or more inputs at close to the same time. If the stimuli come on the same synaptic pathway, this is called homosynaptic, and, if on different synaptic pathways, this is called heterosynaptic. Increased synaptic strength is called long-term potentiation (LTP); decreased synaptic strength is called long-term depression (LTD).

rTMS at slow rates, approximately between 0.2 and 1 Hz, will cause a decrease in brain excitability (Chen et al., 1997). rTMS at faster rates, approximately 5 Hz or faster, will cause an increase in brain excitability (Pascual-Leone et al., 1994). In an animal model of these effects, in the immediate period after rapid or slow rTMS to the cat visuo-parietal cortex, the uptake of (14)C-2DG was increased or decreased, respectively (Valero-Cabre et al., 2007). TMS can also be used repetitively in a mode where very short, very high frequency trains of stimuli are delivered at theta frequency, about 5 Hz. This is called theta-burst stimulation (TBS) (Di Lazzaro et al., 2005; Huang et al., 2005). A typical paradigm would be three stimuli at 50 Hz, repeated at 5 Hz. If given intermittently, say 2 s of stimulation every 10 s, this leads to increased excitability. If given continuously over 40 s, this leads to decreased excitability.

Another method for influencing brain excitability is a low-level continuous electric current, called transcranial direct current stimulation (tDCS). This is becoming a popular technique as well but will not be emphasized here since it is not magnetic. Anodal stimulation will facilitate the motor cortex, and cathodal stimulation will inhibit it.

Heterosynaptic plasticity can be realized in humans with a peripheral stimulus paired with a TMS brain stimulus. A nice set of experimental paradigms has been developed by Classen and collaborators and called paired associative stimulation (PAS) (Stefan et al., 2000; Wolters et al., 2003). If a median nerve stimulus at the wrist is paired with a TMS to the sensorimotor cortex at 25 ms, then the two stimuli arrive at about the same time, and the MEPs will be facilitated (Figure 7). If the interval is about 10 ms, the TMS comes about 15 ms before the median nerve volley arrives, and the MEP will be depressed. The former behaves like LTP and the latter like LTD (McDonnell et al., 2007). As a simple motor learning task and PAS interact with each other, it does appear that PAS is a highly relevant model for brain plasticity (Ziemann et al., 2004).

Comparison with EEG/MEG and Functional Imaging

There are several noninvasive techniques available to neuroscientists these days. Each method gives a different view of brain function. One particular view might be best in a particular situation, but often it will be better to get multiple views for more complete understanding. EEG and MEG are direct measures of neuronal activity, and timing information is excellent, but spatial information is not so good and is even ambiguous because of the nonuniqueness of the inverse problem (determination of sources from the scalp recordings). EEG measures voltage differences from different sites on the scalp. These voltage differences are set up by transmembrane currents, mainly postsynaptic potentials of apical dendrites of large pyramidal cells. Those that are oriented perpendicularly to the surface of the cortex have more influence

Table 1. Summary of Noninvasive Methods for Excitation and Inhibition

Method	Excitatory Mode	Inhibitory Mode
rTMS	high frequency, ≥5 Hz	low frequency, 0.2–1 Hz
TBS	intermittent	continuous
tDCS	anodal	cathodal
PAS	synchronous heterosynaptic stimulation	asynchronous heterosynaptic stimulation

than those oriented tangentially. Scalp potentials will be measured only when a sufficient number of cells are active synchronously, and this synchrony is facilitated by the columnar organization of the cortex. MEG is similar to EEG but measures more the intracellular currents. The sources of MEG may be better localized than with EEG because MEG is not distorted by the skull and scalp, but MEG is blind to radial sources. PET and fMRI are techniques for functional neuroimaging and have good spatial localization but less temporal resolution. PET using O-15 water measures regional cerebral blood flow, and this is a reasonable measure since synaptic activity increases local metabolism and stimulates changes in perfusion. fMRI most commonly uses the BOLD technique, which measures the oxidation state of hemoglobin in the blood. Since with metabolism, blood flow increases more than oxygen extraction, blood becomes more oxygenated. This is a rather indirect measure of neuronal activity, but it does correlate with perfusion measures, and like EEG and MEG, it is most closely correlated with synaptic activity.

One example of how the techniques show different views of a physiological process is what happens in the motor cortex in the no-go trials in a go/no-go experiment. The go/no-go experiment is a two-choice reaction time experiment, to either move or not move, depending on the stimulus. Neuroimaging of the no-go trials themselves, not mixed up with the go trials, is possible with single-event fMRI studies. There is a distinct activation in the M1 region with a go trial, but no similar activation (or deactivation) in the no-go trials (Figure 8) (Waldvogel et al., 2000). This was in contrast to the SMA region, where similar activation was seen in both types of trials. The SMA activation indicated that the brain was clearly involved in the decision making during the no-go trials, but nothing appeared to be happening in M1. Similar studies have been done with EEG (Leocani et al., 2000b). Comparing the go and no-go trials, there is negativity in the M1 region with both, even though there is more with the go trials. Thus, the EEG suggests that something is apparently happening despite the negative fMRI.

Study of the same experiment with TMS clears up the problem. TMS was delivered to the contralateral motor cortex during the reaction time period to explore the change of excitability. The baseline was a small MEP so that inhibition could be detected as well as increased excitability. In the go trials, there was an increase of excitability prior to the movement, and in the no-go trials, there was inhibition (Leocani et al., 2000a; Waldvogel et al., 2000). There is a potential problem, however, in understanding what is happening with a suppression of the MEP amplitude after TMS. There could be simple withdrawal of excitation, or there could be active inhibition. This issue can be addressed with a study of SICI in the reaction time period, and it does turn out that there is active inhibition (Sohn et al., 2002; Waldvogel et al., 2000).

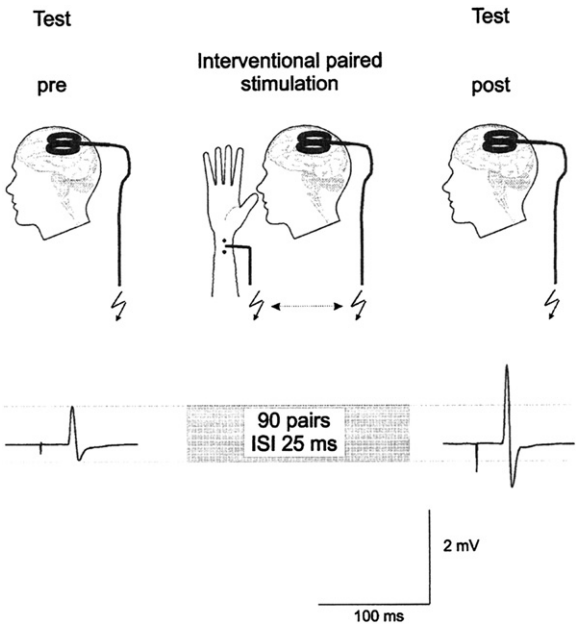

Figure 7. Technique of Paired Associative Stimulation
The method is illustrated in the middle part where 90 pairs of median nerve stimulation and TMS are given with an interstimulus interval (ISI) of 25 ms. The post-test MEP (on the right) has become larger than the pre-test MEP (on the left). From Stefan et al. (2000), with permission.

What appears to be happening in the motor cortex during the no-go trials is active inhibition, as demonstrated clearly by TMS. The EEG detects what is happening and gives information about its time course, but neuroimaging in this situation does not even show that there is activity, and this is likely due to the fact that inhibition is not as demanding a metabolic process as is excitation.

Repetition priming is an aspect of implicit memory where recent exposure to an item leads to more rapid recognition of it upon subsequent exposure. It had been known that this phenomenon is accompanied by a reduction in brain activity seen with fMRI (as well as less neuronal firing seen in nonhuman primates). It was not clear, however, whether this imaging finding was integral to the priming effect or an epiphenomenon. A study was done to assess this using rTMS to interfere with a task making judgments as to whether objects were living or not, a task that shows reduction of activity in the left inferior frontal gyrus (Wig et al., 2005). Left frontal rTMS was given during the presentation of some objects, and left

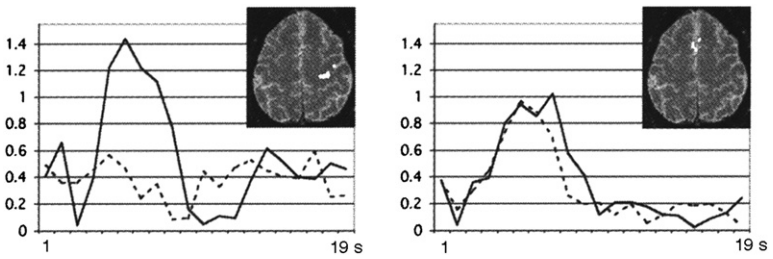

Figure 8. Single-Event fMRI of the Go (Solid Line) and No-Go (Dotted Line) Tasks in a Go/No-Go Reaction-Time Experiment

The left figure shows the time course of activity at M1; the inset shows the area of activation of M1 from the go task, which are the voxels used for the time course. The right figure shows the time course of activity at SMA; the inset shows the area of activation of SMA from the go task, which are the voxels used the time course. From Waldvogel et al. (2000), with permission.

motor cortex rTMS was given during presentation of other objects. Only for those objects with the left frontal rTMS was there the coupled phenomena of reduced priming effect and failure of reduction in fMRI activity.

Neuroimaging has been applied to understand the process of clinical recovery after stroke, and use of EEG and TMS helps to interpret the findings (Rossini and Dal Forno, 2004). In one example, 11 well-recovered chronic stroke patients with left capsular lesions were investigated (Gerloff et al., 2006). Using functional PET, the patients showed enhanced activation of the lateral premotor cortex of the lesioned hemisphere but also the lateral premotor, primary sensorimotor, and parietal cortex of the contralesional hemisphere. Studies with EEG using coherence analysis to demonstrate patterns of connectivity showed that cortico-cortical connections were reduced in the stroke hemisphere but increased in the contralesional hemisphere. However, no direct ipsilateral MEPs could be elicited with TMS over the contralesional primary motor cortex. The conclusion, drawn most clearly from TMS, is that the corticospinal commands come largely from the lesioned hemisphere. Other TMS studies support the same conclusion (Werhahn et al., 2003). Contralesional activity may well play a more direct role when the lesioned hemisphere is badly damaged, but in these well-recovered patients its role may be to operate at a higher-order processing level, similar to what is seen when healthy subjects make complex movements. For example, rTMS interference with the contralesional premotor cortex will cause timing errors in the performance of complex finger movement sequences (Lotze et al., 2006). Compensatory activation of the "contralesional" premotor cortex can also be demonstrated in normal subjects after suppression of one premotor cortex using 1 Hz rTMS (O'Shea et al., 2007).

TMS can be used in conjunction with the other imaging modalities. Functional imaging with either fMRI or PET can show the areas influenced by TMS. In these studies, TMS is delivered either in the scanner or immediately before scanning, and areas that are connected to the stimulated area may show changes in metabolism. Using TMS together with raclopride PET scanning has demonstrated dopamine release in the putamen after stimulation of the motor cortex (Strafella et al., 2003). TMS can be used with EEG, and in this circumstance both immediate and delayed effects of TMS can be demonstrated on cortical function. For example, TMS was used together with high-density EEG to see how activation of the premotor area is transmitted to the rest of the brain during sleep (Massimini et al., 2005). During quiet wakefulness, the initial response at the stimulation site was followed by a sequence of waves in connected cortical areas several centimeters away. During non-rapid eye movement sleep, the initial response did not propagate beyond the stimulation site, indicating reduced functional cortical connectivity during sleep. In another study, cortical responses to single TMS pulses were measured with EEG before and after applying rTMS to motor cortex (Esser et al., 2006). After rTMS, EEG responses were significantly potentiated, consistent with the idea that the TMS induced LTP in the underlying brain area.

The physiology of visuospatial judgments was assessed with fMRI together with disruptive TMS (Sack et al., 2007). Right, but not left, parietal TMS impaired visuospatial judgment and induced fMRI changes in a right hemisphere frontoparietal network. There were significant correlations between the induced behavioral impairment and fMRI changes in both the directly stimulated parietal and remote ipsilateral frontal brain regions. The network identified by TMS was the same as that found during the execution of visuospatial judgments. This study verified the idea that visuospatial deficits following parietal damage are caused by disrupting activity across a network rather than just at a single site.

Clinical Utility

Central motor conduction time delays can be indicative of demyelinating injury to the corticospinal tract. The first useful application was in multiple sclerosis. There have been a large number of studies, most showing a high yield of abnormality even without clinical evidence of corticospinal tract involvement. Comparisons with other tests, such as evoked potentials and MRI, generally show value for TMS studies as well (Beer et al., 1995). Moreover, there appears to be a good correlation of conduction time with disability (Fuhr et al., 2001).

Compressive myelopathy is another good indication for central motor conduction studies. A number of investigations have revealed a high yield. One study investigated 67 patients with cervical spondylosis or disk herniation (Maertens de Noordhout et al., 1991). Central conduction times were abnormal in 84% of patients with, and 22% of those without, radiologic signs of cervical cord compression, while median nerve somatosensory evoked potentials were abnormal in only 25% of patients. MEP

abnormalities correlated with upper motor neuron signs. By investigating MEPs in a series of muscles, it might be possible to localize the level of the cord compression (Chan et al., 1998).

Another clinical use is in stroke. In the acute stage, when the patient is paralyzed, the presence of an MEP is a good prognostic sign (Delvaux et al., 2003). The absence of the MEP in this situation can be a bad sign (Trompetto et al., 2000). The presence of an MEP in the face of paralysis has also been sometimes useful in the diagnosis of psychogenic paralysis (Janssen et al., 1995).

Applications in Pathophysiology

The plasticity of brain in adult life is an exciting area of current neuroscience research, and TMS studies have played a useful role in its elucidation. One model has been amputation of the arm at about the level of the elbow (Ziemann et al., 1998). Motor representation areas targeting muscles ipsilateral and immediately proximal to the stump were larger than those for muscles contralateral to the stump. These results are consistent with the idea that the motor cortex for the muscles proximal to the amputation had expanded into the territory of the amputated part. Some of this plasticity can occur rapidly, as demonstrated in experiments with reversible deafferentation accomplished by using a blood pressure cuff. The amplitudes of MEPs to TMS from muscles immediately proximal to the temporarily anesthetized forearm increased in minutes after the onset of anesthesia and returned to control values after the anesthesia subsided. On the other hand, other plastic processes may take a longer time, as demonstrated in the situation where, after a brachial plexus avulsion, an intercostal nerve is anastomosed to the musculocutaneous nerve. After a year or more, subjects could voluntarily flex their elbows, and projections from the biceps region of the motor cortex were directed to the spinal cord neurons of the intercostal nerve (Mano et al., 1995).

Cortical changes also result from changes in the patterns of behavior. In proficient Braille readers, the representation of the first dorsal interosseous muscle in the reading hand was significantly larger than that in the nonreading hand or in either hand of control subjects (Pascual-Leone et al., 1993). Conversely, the motor cortex area of the tibialis anterior muscle diminished after a period of unilateral immobilization of the ankle joint compared to the unaffected leg, without changes in spinal excitability or motor threshold (Liepert et al., 1995). Some of these changes can occur rapidly. The motor cortical representation of the hand increased over a 5 day period in normal subjects as they learned a skilled task with their hand (Pascual-Leone et al., 1995).

There are several different mechanisms for the genesis of epileptic seizures and for the modes of action of antiepileptic drugs. TMS can give information about these mechanisms by assessing cortical excitability. For example, motor threshold is decreased in untreated patients with idiopathic generalized epilepsy (Reutens et al., 1993). On the other hand, in progressive myoclonic epilepsy, threshold is normal, but there is a loss of cortical inhibition demonstrated with paired-pulses at 100–150 ms and an increase in facilitation at 50 ms interval (Valzania et al., 1999). Similar changes in SICI and ICF may be present in patients with crytogenic epilepsy (Cantello et al., 2000). Specific effects can be seen with various anticonvulsants, as studied in normal subjects (Ziemann, 2004). Vigabatrin and gabapentin, which are GABAergic, increase intracortical inhibition. Carbamazepine, lamotrigine, and phenytoin, which block sodium and calcium channels, elevate motor threshold. Not only can TMS elucidate these mechanisms, but it can potentially be used to quantify physiological effects in individual patients, and this may be more valuable in some circumstances than anticonvulsant blood levels.

Abnormalities of the basal ganglia may give rise to movement disorders, and this is likely in part due to its effect on motor and premotor networks in brain. Studies with TMS have revealed abnormalities in Parkinson's disease, Huntington's disease, and dystonia (Cantello, 2002). For example, in dystonia, there is no change in motor threshold, but there is an increase in the slope of the MEP recruitment curve and a decrease in intracortical inhibition (Hallett, 1998; Ridding et al., 1995). The primary dysfunction seems to be loss of cortical inhibition, and this appears to explain a number of clinical features such as activation of an excessive number of muscles in attempted voluntary movement.

In Parkinson's disease, there is no change in motor threshold. There is an increase in the slope of the MEP recruitment curve, but voluntary contraction produces less facilitation of the MEP than expected. The SP is shortened and can be normalized with therapy. There is a decreased SICI. In Huntington's disease, various abnormalities have been reported, but results are variable, likely because of the influence of the background chorea on the physiological measures. The SP is likely prolonged, reflecting possibly overactive dopaminergic function (Modugno et al., 2001). In Tourette's syndrome, motor threshold is normal, but the cortical silent period is shortened and the intracortical inhibition reduced (Ziemann et al., 1997).

In ataxia, it is possible to find evidence for cerebellar dysfunction with a special type of paired-pulse testing. A magnetic stimulus over the cerebellum reduces the size of responses evoked by magnetic cortical stimulation when it precedes cortical stimulus by 5, 6, and 7 ms. Suppression of motor cortical excitability is reduced or absent in patients with lesions in the cerebellum (Ugawa et al., 1997). The degree of suppression correlates with the severity of ataxia in patients with degenerative late-onset ataxia.

In patients with classic migraine, the threshold for production of phosphenes with TMS is reduced, suggesting hyperexcitability of occipital cortex in this disorder (Afra et al., 1998; Aurora et al., 1998). Studies of suppression of visual stimuli show that migraineurs have less suppression than normal subjects, suggesting less inhibition in the visual cortex (Mulleners et al., 2001).

In Alzheimer's disease, there is deficiency of acetylcholinergic processing. SAI is mediated by muscarinic synapses. SAI has been shown to be deficient in Alzheimer's disease (Di Lazzaro et al., 2004), but not in frontotemporal dementia (Pierantozzi et al., 2004) or mild cognitive impairment (MCI) (Sakuma et al., 2007), and this might be used as a pathophysiologically based biomarker.

Therapeutic Applications

Long-lasting influences on the brain depend on changing synaptic strength or causing anatomical changes such as alterations in dendritic spines or sprouting. Since the anatomical changes may well be a secondary consequence of prolonged changes of synaptic strength, the basic logic of TMS stimulation is to change synaptic strength. Such logic has been applied in many disorders.

Parkinson's Disease

TMS can speed up the reaction time in patients with Parkinson's disease (PD), and this led to the idea that rapid rTMS might be able to be used for therapy. Early studies suggested an improvement in pointing performance after rTMS to the motor cortex (Siebner et al., 1999a) and an improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) with rTMS (Siebner et al., 2000). In another study, subthreshold rTMS applied to the motor cortex at both 0.5 Hz (600 pulses) and 10 Hz (2000 pulses), but not sham stimulation, improved many aspects of motor performance (Lefaucheur et al., 2004). Such changes lasted only for minutes.

A more substantial and long-lasting effect of rTMS therapy appears to come with repeated application over a period of days. Thirty-six unmedicated PD patients were randomized to one of two groups, real-rTMS (suprathreshold 5 Hz, 2000 pulses once a day to the motor cortex for 10 consecutive days) and sham-rTMS (Khedr et al., 2003). TMS improved the total motor section of the UPDRS, walking speed, and self-assessment scale after the sessions were over, and the benefit lasted at least 1 month. In a double-blind placebo-controlled study, eight rTMS sessions were performed over 4 weeks using four cortical targets (left and right motor and dorsolateral prefrontal cortex) in each session, with 300 pulses each, 100% of motor threshold intensity (Lomarev et al., 2006). A therapeutic rTMS effect lasted for at least 1 month after treatment ended. A meta-analysis of 12 studies concluded that the literature does show a positive effect of rTMS on Parkinson motor function (Fregni et al., 2005).

Dystonia

There is a different rationale for rTMS in dystonia. Physiological findings in dystonia reveal a decrease in intracortical inhibition. Since rTMS delivered over the primary motor cortex at 1 Hz can induce an increase in inhibition, this might ameliorate the deficit. An initial study showed a normalization of the intracortical inhibition and some modest improvement in performance (Siebner et al., 1999b). Another target could be the premotor cortex, since rTMS at 1 Hz can ameliorate the deficit in reciprocal inhibition in dystonia (Huang et al., 2004). Nine patients with writer's cramp and seven age-matched control subjects were studied using subthreshold 0.2 Hz rTMS applied to the MC, SMA, or PMC (Murase et al., 2005). Stimulation of the PMC but not the MC significantly improved the rating of handwriting in the patient group. rTMS over the other sites or using a sham coil in the patient group or trials in the control group revealed no clinical changes.

Stroke

Much of the spontaneous recovery from stroke after the acute phase involves plastic changes in the brain. The task for rehabilitation is to find ways to facilitate plasticity so that the changes occur more rapidly and more completely. Since much of good recovery depends on plasticity in the lesioned hemisphere, one therapeutic approach is to try to increase brain plasticity in the lesioned region with brain stimulation. In one study, rTMS or sham stimulation was given over the ipsilesional motor cortex daily for 10 days to two randomly assigned groups of 26 patients with acute ischemic stroke (Khedr et al., 2005a). Disability scales measured before rTMS, at the end of the last rTMS session, and 10 days later showed that real rTMS improved patients' scores more than sham. In another study, 15 patients with chronic hemiparetic stroke practiced a complex, sequential finger motor task using their paretic fingers either after 10 Hz or sham rTMS over the ipsilesional primary motor cortex (M1) (Kim et al., 2006). Both the changes in the behavior and corticomotor excitability before and after the intervention were examined by measuring the movement accuracy, the movement time, and the MEP amplitude. rTMS resulted in a significantly larger increase in the MEP amplitude than the sham rTMS, and the plastic change was positively associated with an enhanced motor performance accuracy.

Another approach to brain stimulation is to target the contralesional side. The contralesional M1 inhibits the ipsilesional M1 via transcallosal inhibition (TCI). One study tested whether a decreased excitability of the contralesional M1 induced by 1 Hz rTMS could cause improved motor performance of the affected hand in stroke patients by decreasing the TCI (Takeuchi et al., 2005). When compared with sham stimulation, rTMS reduced the amplitude of motor-evoked potentials in contralesional M1 and the TCI duration, and rTMS immediately induced an improvement in pinch acceleration of the affected hand, although a plateau in motor performance had been reached by the previous motor training. This improvement in motor function after rTMS was significantly correlated with a reduced TCI duration. Other studies showed similar results (Mansur et al., 2005).

Other Neurological Conditions

There is also some demonstrated efficacy in epilepsy, although most studies are small and the effect generally mild. The logic here has been that the epileptic area is excessively active and should be suppressed. A recent multicenter study showed reduction of interictal discharges, but not a reduction in seizures (Cantello et al., 2007). One of the most successful studies dealt with

patients who had epileptic foci related to regions with malformations of cortical development (Fregni et al., 2006b). Slow rTMS was effective in this group compared with sham stimulation in reducing seizures.

Following the surprising observation that epidural motor cortex stimulation could relieve pain, Lefaucheur and colleagues have done a series of studies looking for efficacy of rTMS over M1. They first reported 18 patients with intractable neurogenic pain of various origins and found a significant decrease in the mean pain level after 10 Hz rTMS (Lefaucheur et al., 2001a). A second study showed improvement in 14 patients with intractable pain due to thalamic stroke or trigeminal neuropathy (Lefaucheur et al., 2001b). Another group investigated whether 5 consecutive days of 20 Hz rTMS would lead to longer-lasting pain relief in unilateral chronic intractable neuropathic pain (Khedr et al., 2005b). Forty-eight patients with therapy-resistant chronic unilateral pain syndromes (24 each with trigeminal neuralgia and post-stroke pain syndrome) had improvement in pain scales, evident even 2 weeks after the end of the treatment.

Some benefit has also been found for some patients with tinnitus with stimulation over the auditory cortex (De Ridder et al., 2005; Kleinjung et al., 2005).

Psychiatric Conditions

The most extensive use of rTMS therapy is for psychiatric conditions, mainly depression. Given the known efficacy of electroconvulsive therapy for depression, the idea arose that rTMS might well be able to deliver equally effective focal therapy more easily and with fewer side effects. As with all applications of rTMS therapy, there are a large number of ways to deliver it, and the optimal location, stimulus frequency, intensity, and duration of treatment have not been settled. Because neuroimaging has shown hypometabolism of depressed patients in the left dorsolateral prefrontal cortex, therapy has generally been directed to that region with excitatory stimulation. A smaller number of studies have used inhibitory (slow) rTMS to the right dorsolateral prefrontal cortex instead. A recent meta-analysis evaluated 33 studies and found that active rTMS treatment was efficacious (Herrmann and Ebmeier, 2006). There was high variability among studies, and this was thought to be likely due to the differences in technique. In these studies all together, there were 475 patients treated with active stimulation and 402 patients treated with sham stimulation. For active stimulation, there was a mean reduction of 33.6% in depression scores, while for sham stimulation there was a reduction of 17.4%. They found no feature predictive of response. In another review of six independent clinical trials, the investigators concluded that better efficacy was related more to patient variables (Fregni et al., 2006a). Patients were more likely to respond if younger or more medication responsive. It must be pointed out, however, that not all studies, and not even all reviews, have a favorable view of rTMS therapy (Couturier, 2005).

Few studies have been conducted in schizophrenia, and conclusions are less secure. Perhaps the best effect is on the reduction of auditory hallucinations after slow rTMS over auditory cortex (Haraldsson et al., 2004). There can also be a reduction in psychotic symptoms after high-frequency stimulation over left prefrontal cortex.

Conclusion and Perspectives

TMS is an excellent physiological tool and complements other noninvasive methods for studying human brain physiology. Motor and sensory function have been obvious areas of investigation, and much more work in the future will be on progressively more complex aspects of human cognition and behavior. As new coils and new patterns of stimulation are developed, there will be even more innovative ways to use this technique. Combined noninvasive techniques can be used in imaginative ways. For example, EEG could be used as a way to determine the time and place to deliver a TMS pulse for maximum advantage. TMS also adds more power to the clinical neurophysiologist for diagnosis of neurological disorders. In regard to therapy, there are clear effects, but most of these are mild and often transient, and there is no approved indication yet in the USA. Further development will be needed to make effects more robust and longer lasting.

ACKNOWLEDGMENTS

The NIH holds the patent for the H-coil, and I am one of its coinventors.

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