

Transcranial magnetic stimulation and the human brain

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Transcranial magnetic stimulation (TMS) is rapidly developing as a powerful, non-invasive tool for studying the human brain. A pulsed magnetic field creates current flow in the brain and can temporarily excite or inhibit specific areas. TMS of motor cortex can produce a muscle twitch or block movement; TMS of occipital cortex can produce visual phosphenes or scotomas. TMS can also alter the functioning of the brain beyond the time of stimulation, offering potential for therapy.

It was just two decades ago that Merton and Morton surprised neuroscientists by showing that it was possible to stimulate the motor areas of the human brain electrically through the intact scalp (transcranial electrical stimulation, TES)¹. They used a brief, high-voltage electric shock to activate the motor cortex and produce a relatively synchronous muscle response, the motor evoked potential (MEP). It was immediately clear that this would be useful for many purposes, but a problem with TES is that it is painful because of activation of pain fibres in the scalp. Five years later, Barker and colleagues showed that it was possible to stimulate both nerve and brain using external magnetic stimulation (TMS; see Box 1), with little or no pain². TMS is now commonly used in clinical neurology to study central motor conduction time (Box 2). Depending on stimulation parameters, TMS can excite or inhibit the brain, allowing functional mapping of cortical regions and creation of transient functional lesions. It is now widely used as a research tool to study aspects of human brain physiology including motor function, vision, language and the pathophysiology of brain disorders. It may even be useful for therapy, particularly in psychiatry.

Interruption of brain activity

There are several complementary methods that can be used to study the contribution of cortical networks to specific cognitive functions. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have revealed the brain networks involved in specific functions. However, these methods lack time resolution and cannot alone prove that an area is essential for a particular function. TMS can transiently disrupt activity in focal brain regions, allowing researchers to assess function on a milli-second scale. TMS studies, unlike functional imaging, can also be frequently repeated.

In the visual system, TMS has been used to study perception. Whereas strong TMS of occipital cortex can produce phosphenes, a stimulus of lower intensity can induce a transient scotoma. In the initial demonstration, subjects were shown brief, randomly generated letters on a visual monitor, and TMS was delivered after the visual stimulus³. When TMS was delivered 80–100 ms after the stimulus, subjects saw a blur or nothing at all, indicating that important visual processing during that time interval had been interrupted. Subsequent studies with more sensitive techniques indicated an additional, earlier period of suppression corresponding to the initial arrival of visual information in occipital cortex⁴. In higher cortical areas, TMS can be used to tease apart specialized processing mechanisms. For example, TMS of area V5 can selectively interfere with the perception of motion of a stimulus without impairing its recognition⁵, supporting the hypothesis, originally proposed following imaging studies, that V5 is the motion perception region of the brain.

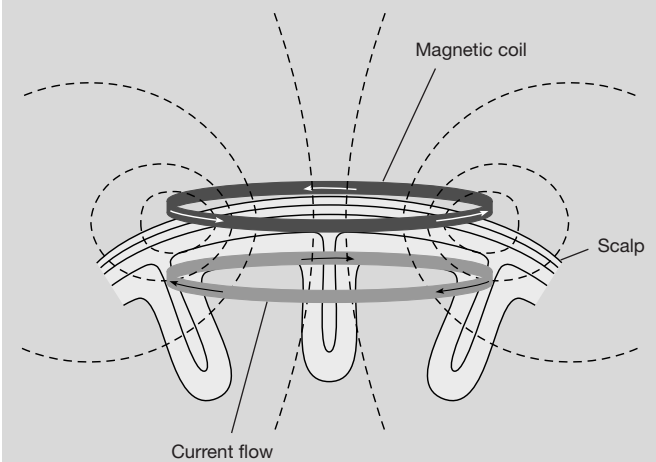
Different aspects of motor control have also been studied using TMS. In a reaction time task, a strong TMS just before the expected motor response can delay the response without altering its form⁶. High-frequency stimulation over the supplementary motor area (SMA) impairs accuracy in complex, but not simple, sequences of

Box 1

Physics and mechanism of action of TMS

For magnetic stimulation a brief, high-current pulse is produced in a coil of wire, called the magnetic coil, which is placed above the scalp. A magnetic field is produced with lines of flux passing perpendicularly to the plane of the coil (see Figure). An electric field is induced perpendicularly to the magnetic field. In a homogeneous medium, the electric field will cause current to flow in loops parallel to the plane of the coil. The loops with the strongest current will be near the circumference of the coil itself. The current loops become weak near the centre of the coil, and there is no current at the centre itself. Magnetic coils may have different shapes. Round coils are relatively powerful. Figure-eight-shaped coils are more focal, producing maximal current at the intersection of the two round components. The precise extent of neuronal activation is not known, but it clearly varies with the intensity of stimulation. TMS ordinarily does not activate corticospinal neurons directly; rather it activates them indirectly through synaptic inputs. This has been determined by the observation that TMS produces a corticospinal volley with indirect waves (I-waves) rather than with an early direct wave (D-wave)³⁹.

Single-pulse TMS, which is very safe, has been most commonly used. Devices are now available that can deliver high-frequency (1–30 Hz), repetitive TMS (rTMS). This has greater effects than single-pulse TMS, but also has the potential to cause seizures even in normal individuals. Safety guidelines have been published which should prevent problems⁴⁰.



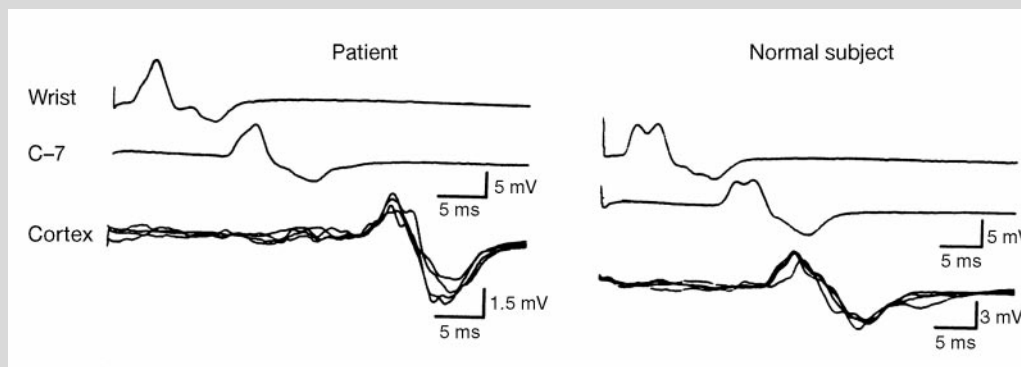
Box 2

Central motor conduction and clinical uses

With TMS, it is possible to study the speed of conduction in central motor pathways. This method has been applied in the evaluation of patients with multiple sclerosis, where there is frequent involvement of the corticospinal tract. Slowing of conduction is also commonly seen in degenerative diseases, however, making the test non-specific. Assessment of central conduction time is a useful method to evaluate neurological disturbance in patients with cervical spondylosis, where even subclinical motor disturbances can be detected⁴¹. TMS can also be used to monitor central motor tracts during spinal cord surgery.

The figure shows the results of tests of central motor conduction to the

abductor digiti minimi (ADM) muscle in a patient with extradural spinal cord compression and a normal subject. The traces show electromyogram recordings from the ADM muscle. From the top down, the responses were elicited by stimulation of the ulnar nerve at the wrist, stimulation at the C-7 level of the spinal cord (activating the nerve roots), and TMS of the cortex over the hand area, respectively. Note that the latencies of the potentials are similar in the patient and normal subject following stimulation at the wrist and spine, but the latency is much longer following cortex stimulation in the patient, implying prolonged central conduction time. With permission from Brunhölzl and Claus⁴¹.



finger movements⁷. The errors in the latter test occurred not in elements of the sequence occurring at the time of the stimulation, but in later elements. These data support a critical role for the SMA in organizing forthcoming movements in complex motor sequences.

In patients with epilepsy who are being investigated for possible temporal lobectomy, it is crucial to know which side of the brain they use for language processing. The standard test for this is the Wada test—amytal is injected into each carotid artery to suppress hemispheric function, and the side on which speech arrest is produced is determined. TMS could provide a simpler alternative test. Lateralized speech arrest can be produced using repetitive TMS (rTMS) with rates from 8 to 25 Hz for 10 s and a coil position over the left (in most people) inferior frontal region⁸. Epstein *et al.* found that speech arrest could be obtained reliably with a repetition rate of 4 Hz, an intensity of 150% motor threshold or less, and pulse trains of no more than 5-s duration over the region that gives the best motor responses for facial muscles⁹. With current techniques, however, for reasons that are unclear, the Wada and rTMS tests do not always agree.

Cortical physiology

TMS can be used to measure various parameters in motor cortex, allowing us to evaluate different aspects of cortical excitability¹⁰. Such measures are useful in understanding the changes in brain physiology seen in the setting of cortical plasticity and brain disorders. For example, the threshold for producing an MEP in resting muscle reflects the excitability of a central core of neurons, which arises from the excitability of individual neurons and their local density. As it can be influenced by drugs that affect sodium and calcium channels, threshold must indicate membrane excitability. Another measure, the recruitment curve, is the growth of MEP size as a function of stimulus intensity. This measurement is less well understood, but must involve neurons other than those in the core region that is activated at threshold. These neurons have higher threshold for activation, either because they are intrinsically less excitable or because they are further from the centre of activation by the magnetic stimulus, and would be part of the 'subliminal fringe'.

Intracortical inhibition (ICI) and facilitation (ICF) are obtained using paired-pulse studies and reflect the activity of interneurons in the cortex¹¹. In such studies, an initial conditioning stimulus is given that is large enough to activate cortical neurons but small enough that no descending influence on the spinal cord can be detected. A second test stimulus, at suprathreshold level, follows after a short time. 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, the MEP is inhibited, and at intervals between 8 and 30 ms it is facilitated. ICI is probably largely mediated by neurons containing γ -aminobutyric acid (GABA). The silent period is a pause in ongoing voluntary electromyogram activity produced by TMS. Although the first part of the silent period is due in part to spinal cord refractoriness, the latter part is entirely due to cortical inhibition. ICI seen with paired pulse stimulation and the silent period reflect different aspects of cortical inhibition.

Brain plasticity

The plasticity of the mature brain—the processes involved in neural repair, and learning and memory—is one of the most exciting areas of neuroscience research today, and TMS studies have been useful in its elucidation in humans. Cohen *et al.* used TMS to study patients with traumatic, surgical or congenital amputations of the arm at about the level of the elbow¹². The areas of motor cortex targeting muscles ipsilateral and immediately proximal to the stump were larger than those for muscles contralateral to the stump (Fig. 1). These results, seen also with PET¹³, are consistent with the idea that the representation in the motor cortex of the muscles proximal to the amputation had expanded into the territory of the amputated part. An alternative interpretation is that the cortical region had become more excitable, but the expansion model is consistent with the results of animal studies using microstimulation¹⁴.

At least some of this plasticity can occur rapidly, as demonstrated in experiments in which a blood pressure cuff is used to induce reversible deafferentation. The amplitudes of MEPs produced in response to TMS in muscles immediately proximal to the temporarily anaesthetized forearm increased minutes after the onset of

anaesthesia and returned to control values after the anaesthesia subsided. On the other hand, other plastic processes may take a longer time. Mano and colleagues studied patients who had totally denervated arms after traumatic accidents and rerouting of a chest wall nerve to the biceps muscle¹⁵. They showed that projections from the biceps region of the motor cortex can be directed to the spinal cord neurons of the chest wall nerve, but this process took a year or more to occur. Expansion of the hand area was demonstrated with TMS and confirmed with PET in patients with facial palsy, showing that motor de-efferentation by itself is sufficient to trigger reorganization¹⁶.

Cortical changes also result from changes in patterns of behaviour. Indeed, it appears that there is a constant battle for the control of each neuron among its various inputs. Pascual-Leone *et al.* used focal TMS to perform detailed mapping of the motor cortical areas targeting two finger muscles, the first dorsal interosseous (FDI) and the adductor digiti minimi (ADM), bilaterally in Braille readers and blind controls¹⁷. In the controls, the motor representations of the right and left FDI and ADM were not significantly different. However, in the proficient Braille readers, the representation of the FDI in the reading hand was significantly larger than that in the nonreading hand or in either hand of the controls. Conversely, Liepert and colleagues studied cortical plasticity in patients who had a unilateral immobilization of the ankle joint without any peripheral nerve damage¹⁸. The motor cortex area of the inactivated tibialis anterior muscle diminished compared to that of the unaffected leg without changes in spinal excitability or motor threshold. In a Braille reader who took a 10-day holiday from reading, the size of the finger representation shrank dramatically until she returned to work—in fact, even time off over the weekend reduced the representation quantitatively¹⁹.

To find out how quickly such changes can occur, Pascual-Leone and colleagues looked at the motor cortical representation of the hand over a five-day period in normal subjects as they learned a skilled task with their hand²⁰. As subjects improved on a five-finger exercise on a piano, the size of the motor representation of the hand increased.

The changes resulting from proficiency in Braille reading are accompanied by other compensatory changes in blind individuals who have been deprived of vision for many years. Sadato *et al.* studied regional cerebral blood flow (rCBF) in a group of subjects blind since early infancy and a group of sighted volunteers performing the same tactile discrimination task, and found that this task activated visual primary and association areas only in the blind²¹. These results were interpreted as indicating that cortical areas normally reserved for vision may be activated by other sensory modalities in blind individuals, but the functional neuroimaging study by itself could not prove that the activation was functionally useful in the discrimination process. To address this question, Cohen *et al.* used rTMS over different scalp positions while blind and sighted subjects performed tactile identification of Braille and Roman letters²². In the blind subjects, stimulation of occipital regions induced more errors in the reading task than stimulation of any other region or stimulation in control subjects, providing firm evidence that the occipital areas are an essential component of the network involved in Braille reading in the blind. Although only a non-significant increase in errors was produced in the normal subjects with occipital stimulation, in a different somatosensory task, discrimination of grating orientation, rTMS over occipital cortex did significantly disrupt function in a normal group²³. This might reflect a more important role of visual imagery in this task.

Brain excitability in neurologic disorders

There are several different mechanisms for the genesis of epileptic seizures and for the modes of action of antiepileptic drugs. TMS can be used to give information about these mechanisms by measuring cortical excitability. For example, motor threshold is

decreased in untreated patients with idiopathic generalized epilepsy²⁴. 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 ms²⁵. Specific effects can be seen with various anticonvulsants in normal subjects²⁶. Vigabatrin and gabapentin, which stimulate GABA receptors, increase intracortical inhibition; whereas 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 can give rise to movement disorders, and this is probably in part due to their effect on motor and premotor networks in brain. Studies with TMS have revealed abnormalities in Parkinson's disease, Huntington's disease and dystonia. 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^{27,28}. 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 movements.

Therapeutic uses

Delivery of multiple single pulses of TMS to the brain does not appear to leave any lasting effect. But rTMS can produce effects that last after the stimulation period. This was first demonstrated in the motor system. Rapid rTMS, at frequencies of 5 Hz and higher, will transiently enhance motor excitability²⁹, whereas slow rTMS, at 1 Hz, will transiently depress excitability³⁰. The mechanisms of these changes are not clear, but the analogies to long-term potentiation (LTP) and long-term depression (LTD) of individual synapses in the central nervous system are apparent.

The observation that TMS, delivered in just the right way, can speed up the reaction time in patients with Parkinson's disease led to the idea that rTMS might be useful for therapy³¹. In an initial trial using a motor coordination task, this seemed to be the case³¹, but the finding was not reproduced³². On the other hand, another study has

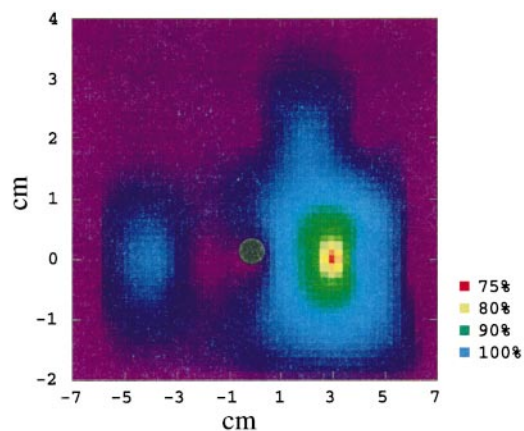


Figure 1 TMS mapping of left and right biceps from a 78-year-old subject 11 months after a left upper limb amputation. The map shows a portion of the scalp, with the top of the figure towards the front and the left side towards the left; the black dot is Cz, indicating the standard position in electroencephalography at the middle of the vertex. The map of the left biceps is over the right hemisphere, and the map of the right biceps is over the left hemisphere. Thresholds for activation at different scalp locations are indicated. Note that the muscle representation area for the left biceps is larger than that for the right biceps and that the threshold for activation of the left biceps was lower than that for the right biceps. Modified with permission from Hallett *et al.*¹².

suggested an improvement in pointing performance after rTMS³³. A different rationale was developed for why rTMS might be useful in dystonia. Physiological findings in dystonia reveal an decrease in intracortical inhibition. As rTMS delivered over the primary motor cortex at 1 Hz can increase inhibition, it was proposed that it might ameliorate the deficit. A study showed normalization of the intracortical inhibition and a modest improvement in performance³⁴.

Following the observation that rTMS might affect mood in normal individuals, a number of groups sought to determine whether rTMS might be effective in the treatment of mood disorders. Early observations have indicated that high-rate rTMS applied to the left dorsolateral prefrontal cortex may improve depression, giving hope that this might replace electroconvulsive shock treatment (ECT)^{35,36}. Conversely, low-rate rTMS delivered to the right dorsolateral prefrontal cortex may also be helpful³⁷. Therapeutic effectiveness depends on the exact site of stimulation, intensity and the precise pattern of pulses including rate, train length, intertrain interval and number of trains. This is clearly difficult to clarify and is currently a very active area of psychiatric research.

The future

Single-pulse TMS is easy to employ because it is noninvasive, non-painful and safe. It can probe the function of many different parts of the cerebral cortex, excite, inhibit and assess aspects of excitability. Its use will probably expand as it clearly supplements other tools that are used to examine human physiology, such as functional neuroimaging. PET or fMRI studies done during TMS might be able to identify the areas of brain activated by TMS and those regions functionally connected to the stimulated sites, allowing evaluation of *in vivo* anatomical connectivity³⁸. It will probably be used more particularly in the area of higher cortical function and in the assessment of drug effects. High frequency rTMS may have significant adverse effects, but when used safely, it will also find specific utility. As a therapeutic device, there are many possibilities, including some not explored yet. If it ultimately proves useful for treatment of depression, TMS may well become a standard medical tool. □

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