Transcranial magnetic stimulation in neurology

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Transcranial magnetic stimulation (TMS) is a non-invasive tool for the electrical stimulation of neural tissue, including cerebral cortex, spinal roots, and cranial and peripheral nerves. TMS can be applied as single pulses of stimulation, pairs of stimuli separated by variable intervals to the same or different brain areas, or as trains of repetitive stimuli at various frequencies. Single stimuli can depolarise neurons and evoke measurable effects. Trains of stimuli (repetitive TMS) can modify excitability of the cerebral cortex at the stimulated site and also at remote areas along functional anatomical connections. TMS might provide novel insights into the pathophysiology of the neural circuitry underlying neurological and psychiatric disorders, be developed into clinically useful diagnostic and prognostic tests, and have therapeutic uses in various diseases. This potential is supported by the available studies, but more work is needed to establish the role of TMS in clinical neurology.

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With any new medical tool we ought to ask ourselves what it can offer that established methods do not for diagnostic, prognostic, and therapeutic parts of clinical neurology. A new neurological tool might have several benefits: establishment of a differential diagnosis earlier or with greater certainty for a given clinical presentation than existing methods; better prediction of the likely course of the disease; further support for sustained and intensive interventions; help in identification of the most suitable treatment strategy; or improvement of clinical outcome as a therapy, itself. Transcranial magnetic stimulation (TMS) promises to be relevant in all these ways. However, most of the potential of this technique is only hinted at by the work done to date. Despite this promise there have been no carefully designed clinical trials to back it up. The aim of this review is to highlight these exciting possibilities and hopefully engage an interest that will lead to the completion of appropriate studies to assess the true clinical value of TMS in neurology.

Basic principles of magnetic stimulation

TMS, as currently used, was introduced by Anthony Barker (University of Sheffield, UK) in 1985.[1] TMS provided, for the first time, a non-invasive, safe, and—unlike transcranial electrical stimulation (TES)—painless[2] method of activating the human motor cortex and assessing the integrity of the central motor pathways. Since its introduction, the use of TMS in clinical neurophysiology, neurology, neuroscience, and psychiatry has spread widely, mostly in research applications, but increasingly with clinical aims in mind.[3–6]

TMS is based on the principle of electromagnetic induction, as discovered by Michael Faraday in 1838. If a pulse of current passing through a coil placed over a person's head has sufficient strength and short enough duration, rapidly changing magnetic pulses are generated that penetrate scalp and skull to reach the brain with negligible attenuation. These pulses induce a secondary ionic current in the brain (figure 1). The site of stimulation of a nerve fibre is the point along its length at which sufficient current to cause depolarisation passes through its membrane. The capacity of TMS to depolarise neurons depends on the "activating function",[7] which causes transmembrane current to flow and can be described mathematically as the spatial derivative of the electric field along the nerve. Thus, stimulation will take place at the point where the spatial derivative of induced electric field is maximum (figure 1).[7–9] In the case of a bent nerve, the situation is a little different: although the fibre bends across the induced electric field, the current will continue in a straight line and pass out of the fibre across the membrane (figure 1). Thus, the spatial derivative of the electric field along the nerve is critical, again causing a bend to be a preferential point of stimulation. These characteristics of TMS cause it to differ from TES in several ways. Measurements from the surface of the spinal cord have shown that both types of stimuli can evoke an early spike called a direct wave and up to four further spikes, termed indirect waves. However, depending on the orientation of the current induced in the brain, TMS will preferentially activate the pyramidal cells indirectly (ie, trans-synaptically) to evoke indirect waves, or at their axon hillock directly to cause direct waves.[10,11] For TMS, fast-conducting axons (>75 m/s) have a lower threshold for direct waves, whereas slow-conducting axons (<55 m/s) have a lower threshold for indirect waves. For TES, most axons have lower threshold for direct waves than for indirect waves or similar threshold for both types of wave. In addition, with strong TES stimuli the site of activation will shift below the cortex, while TMS will still excite axons mostly within the cortex even at high stimulation intensity.[12] This property of TMS makes it particularly well suited to the study of excitability (responsiveness to

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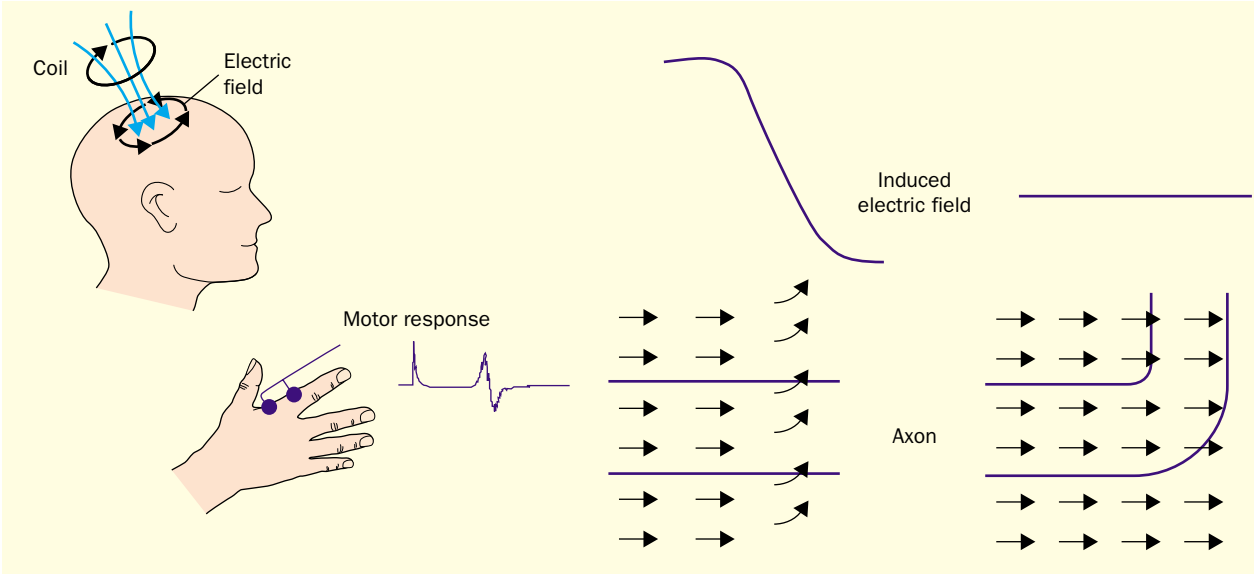

Figure 1. Principle of TMS. Left: the current flowing briefly in the coil generates a changing magnetic field that induces an electric current in the tissue, in the opposite direction. Middle: schematic illustration of the current flow due to the induced electric field that changes along the length of a nerve fibre and results in a transmembrane current. Right: a bent nerve and the uniform current in the uniform electric field also results in a transmembrane current.

stimulation) in the brain cortex. Some neurological disorders may involve or be caused by an impairment of cortical excitability or altered interactions between cortical and subcortical structures, which can be detected by TMS. Furthermore, TMS can be used to modify intracortical excitability and activate distant cortical, subcortical, and spinal structures along specific connections. However, there are questions about the specific cellular effects of TMS, and further animal studies are required to clarify the precise mechanisms of action of TMS. For the clinical applications that we aim to discuss here, such questions are less critical than for studies aimed at increasing our understanding of human cortical physiology and brain–behaviour relations.

During TMS, the operator can control the intensity of the stimuli by changing the intensity of current flowing in the coil, thus changing the magnitude of the induced magnetic field and of the secondarily induced electrical field. The focus of the magnetic field depends on the shape of the stimulation coil. Two different shapes of coils are most commonly used—a figure-of-eight shaped coil and a circular coil. The former provides a more focal stimulation, allowing fairly detailed mapping of cortical representation.[13] The latter induces a more widely distributed electric field allowing for bihemispheric stimulation, which is particularly desirable in the study of central motor conduction times.[14,15] In addition to its intensity and focus, operators can also control the frequency of the delivered stimuli, which will critically determine the effects of TMS on the targeted region of the brain. Of course, the location of a stimulation coil is also dependent on the operator: different brain regions can be stimulated to evoke different behavioural effects. Anatomically precise localisation of stimulation can be achieved by use of a frameless stereotactic system.[16–18]

Diagnostic and prognostic applications of TMS

TMS delivered to different levels of the motor system (neuraxis) can provide information about the excitability of the motor cortex, the functional integrity of intracortical neuronal structures, the conduction along corticospinal, corticonuclear, and callosal fibres, as well as the function of nerve roots and peripheral motor pathway to the muscles. The patterns of findings in these studies can help to localise the level of a lesion within the nervous system, distinguish between a predominantly demyelinating or axonal lesion in the motor tracts, or predict the functional motor outcome after an injury. The abnormalities revealed by TMS are not disease-specific and the results should be interpreted in the context of other clinical data. Some TMS findings can be quite useful for an early diagnosis (eg, multiple sclerosis, Bell's palsy, psychogenic paresis, plexus neuropathy) and prognostic prediction (eg, multiple sclerosis, stroke, cervical spondylosis; table[19–50]). However, what TMS can add to detailed, serial neurological exams has yet to be ascertained.

Motor threshold

When TMS is applied to the motor cortex at appropriate stimulation intensity, motor evoked potentials (MEPs) can be recorded from contralateral extremity muscles. Motor threshold refers to the lowest TMS intensity necessary to evoke MEPs in the target muscle when single-pulse stimuli are applied to the motor cortex. In most recent TMS studies, motor threshold is defined as the lowest intensity required to elicit MEPs of more than 50 μV peak-to-peak amplitude in at least 50% of successive trials, in resting or activated (slightly contracted) target muscles.[51] Motor threshold is believed to reflect membrane excitability of corticospinal neurons and interneurons projecting onto these neurons in the motor cortex, as well as the excitability of motor neurons in the spinal cord, neuromuscular junctions and muscle.[52] In

addition to the membrane excitability itself, motor threshold must also relate to the activity of neural inputs into pyramidal cells that affect their membrane excitability (ie, tonic inhibitory and excitatory drives onto the cortical output neurons). Ultimately, motor threshold provides insights into the efficacy of a chain of synapses from presynaptic cortical neurons to muscles. Motor threshold is often increased in diseases that can affect the corticospinal tract, such as multiple sclerosis, stroke, and brain or spinal-cord injury.[23,32,41,42] Patients with amyotrophic lateral sclerosis show lower motor threshold than healthy people and increased excitability of hand motor area at an early stage of their disease while hand muscle function is normal.[43,46] When the disease progresses and lower motor neuron or mixed signs appear in the hand muscles, the motor threshold generally rises, suggesting a loss of upper motor neurons or affected peripheral nerves.[53] Even when patients with amyotrophic lateral sclerosis do not show clinical corticobulbar signs, TMS can detect involvement of the pathways to muscles supplied by cranial nerves (increased motor threshold, delayed central motor conduction time, and reduced silent period).[54]

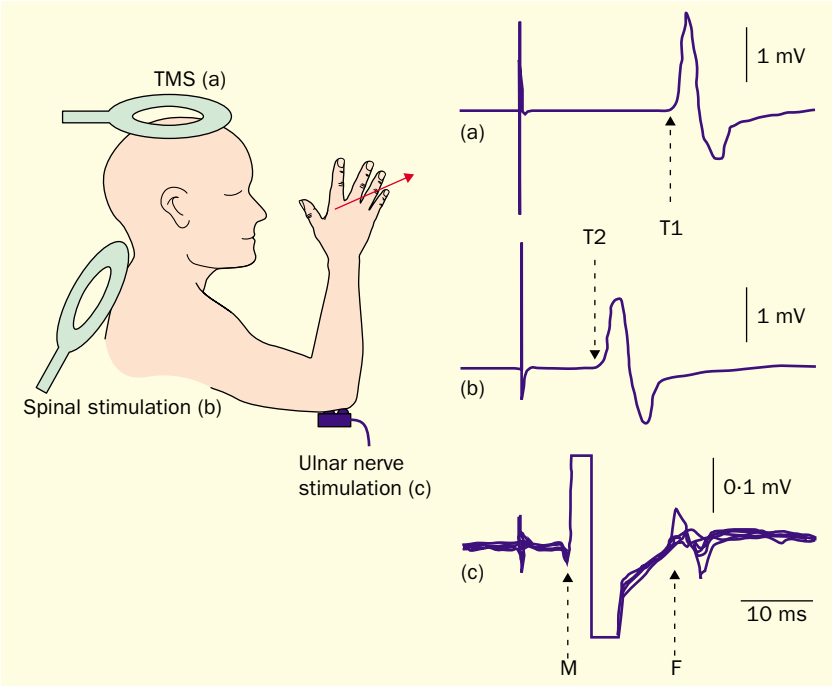

Figure 2. Schematic representation of the calculation of central motor conduction time (CMCT). (a) Motor evoked potential induced by TMS. (b) MEP after cervical spinal root stimulation. (c) F-waves after ulnar nerve electric stimulation. CMCT is estimated by onset latency of T1 minus onset latency of T2. By use of F-wave latency CMCT can be estimated more precisely as T1-(F+M-1)/2. T1= onset latency of MEP elicited by TMS; T2= onset latency of MEP elicited by the coil placed on the back of cervical spine. M= onset latency of M-wave by electrical ulnar nerve stimulation. F= onset latency of F-wave by electrical ulnar nerve stimulation.

Single-pulse TMS applied over the occipital lobe can elicit phosphenes in many individuals. Analogous to the motor threshold, a "phosphene threshold" can be determined and used to study the occipital cortex and the visual pathways. Studies have investigated phosphene thresholds in patients with migraine (both with and without visual aura).[55,56] Phosphene thresholds are significantly lower in patients with migraine (greater visual cortical excitability) than control individuals even in asymptomatic intervals. Mulleners and co-workers[57] have gone as far as suggesting that the phosphene thresholds may prove useful in the monitoring of antimigraine-medication efficacy. More work is needed to assess whether such a method would have anything to add to the clinical follow-up and assessment, but clearly TMS seems to be a useful tool for the study of the pathophysiology of migraine aura.

Central motor conduction time

Central motor conduction time is defined as the latency difference between the MEPs induced by stimulation of the motor cortex and those evoked by spinal (motor root) stimulation and is calculated by subtracting the latency of the motor potential induced by stimulation of the spinal motor root from that of the response to motor-cortex stimulation (figure 2). When a TMS coil is placed over the back of the neck or lumbosacral spine, the magnetic pulse will stimulate spinal roots but not the descending spinal tracts themselves.[58,59] Bone is a major governor of induced current in the human body owing to its extremely low conductivity. At the neural foramina of the spine, the induced electric field and its first spatial derivative increase remarkably while in the spinal canal they are small.[60] Studies have shown extreme difficulty in stimulating spinal cord with magnetic stimulation[61] and a lack of latency shift of elicited MEPs, even when moving the coil along the rostrocaudal axis of the spine.[62,63] The central motor conduction time calculated from the data of magnetic stimulation, therefore, includes the true time for central motor conduction plus at least one synaptic delay at the spinal level and time from the proximal root to the intervertebral foramen. More precise central conduction time can be calculated by use of F-wave latency instead of spinal root TMS.[51]

Pronounced lengthening of central motor conduction time suggests demyelination of pathways, while low-amplitude responses with little delay or absence of responses are more suggestive of loss of neurons or axons. Multiple sclerosis and cervical spondylitic myelopathy are typical diseases that show a long conduction time with dispersed and attenuated responses,[20,41,64] whereas in patients with amyotrophic lateral sclerosis, MEPs are of low amplitude but central motor conduction time is only mildly delayed.[43,64] This measure is also related to

Diagnostic applications of TMS

TMS measure	Abnormal findings	Diseases and symptoms
CMCT[19]	Long	MS,[20] ALS, stroke,[21] secondary parkinsonism,[22] secondary dystonia,[22] brain injury, SCI or CS[23]
MEP[15]	Dispersed	MS, stroke[24]
	Small or absent	MS, ALS, stroke,[19,21] brain injury, SCI or CS,[23] hydrocephalus, Bell's palsy[25]
	Large	Parkinson's disease, dystonia[26,27,28]
MEP with triple stimulation technique[29]	Central conduction failure*	MS, ALS (with upper-neuron damage), stroke, secondary parkinsonism, brain injury, SCI or CS, hydrocephalus
Silent period[30]	Long	MS, stroke†,[31] brain injury,[32] SCI or CS, polyradiculitis, demyelinating polyneuropathy,[33] epilepsy[34]
	Short	ALS, Parkinson's disease,[22,35] dystonia,[26,27] agenesis of corpus callosum
	Absent	SCI or CS[36]
Interhemispheric conduction[37,38]	Long latency‡	MS, stroke, brain injury (with transcallosal lesion), dysgenesis of corpus callosum, hydrocephalus
	Reduced interhemispheric inhibition	MS, ALS[39,40]
	Interhemispheric inhibition absent	Stroke (with transcallosal lesion), dysgenesis of the corpus callosum, hydrocephalus
Motor cortex excitability	High motor threshold§[32,41,42]	MS, stroke, agenesis of corpus callosum, brain injury, spinal cord injury, CS
	Low motor threshold§	ALS,[25] hydrocephalus,[44] epilepsy[45]
	Increased intracortical inhibition	Early-stage ALS[46,47,48]
	Decreased intracortical inhibition	Parkinson's disease,[35,49,50] SCI or CS, epilepsy
	Enlarged cortical representation	Dystonia[22,28]

CMCT=central motor conduction time; MS=multiple sclerosis; ALS=amyotrophic lateral sclerosis; SCI=spinal cord injury; CS=cervical spondylosis; MEP=motor evoked potential. *Central conduction failure indicates smaller size of the test MEP than that of control examined by TST. †Prolonged duration with normal MEP and CMCT may be observed in the motor syndrome with exaggerated inhibition within the motor cortex, resembling motor neglect. ‡The latency for transcallosal inhibition (ipsilateral silent period) following single-pulse TMS (figure 4). §High or low value of the motor threshold indicates that they are higher or lower compared with intact hemisphere or normal individuals.

the grade of motor deficits after stroke.[65] Measurement of central motor conduction time can provide supporting evidence for the diagnosis and can also be used as objective markers of disease progression and prognosis.[19,21,66] However, changes in this feature are not specific for any one particular disease.

Motor evoked potentials

The amplitude of the MEP reflects not only the integrity of the corticospinal tract but also the excitability of motor cortex and nerve roots and the conduction along the peripheral motor pathway to the muscles. Patients with dysfunction at any level along the corticospinal pathway may show abnormal MEPs (table), while the presence of intact MEPs suggests integrity of the pyramidal tract. For example, contralateral MEPs acutely after a stroke relate to a favourable recovery, while the absence of MEPs suggests a poor outcome.[21]

The reduced amplitude of MEPs is associated with a central motor conduction failure in many cases, but even in healthy people the size and latency of MEPs shows great interindividual and intraindividual variability, leading to a broad range of normal values; therefore, results are qualitative rather than quantitative. Magistris and colleagues[29,67] developed a "triple stimulation technique", which provides a quantitative electrophysiological measurement of the central motor conduction failure. Peripheral stimuli applied to the brachial plexus (Erb's point) and median nerve at the wrist induce nerve potentials that travel to the spinal cord and collide with the descending corticospinal volleys evoked by TMS of the motor cortex. These collisions of central and peripheral impulses at the peripheral motor neurons suppress the desynchronisation of MEPs caused by the multiple descending volleys evoked by TMS (figure 3). The triple stimulation technique provides new insights into corticospinal tract conduction of healthy individuals and, when applied to patients with corticospinal dysfunction, is 2·75 times more sensitive than conventional MEPs in detecting corticospinal conduction failures. However, the triple stimulation technique is technically challenging and further studies are required to assess its effectiveness in diagnosis, severity assessment, and monitoring of clinical progression and the effects of treatment.

Silent period

When an individual is instructed to maintain muscle contraction and a single suprathreshold TMS pulse is applied to the motor cortex contralateral to the target muscle, the electromyographic activity is arrested for a few hundred milliseconds after the MEP (figure 4). This period of electromyographic suppression is referred to as a silent period, normally defined as the time from the end of the MEP to the return of voluntary electromyographic activity. However, it is difficult at times to define the end of the MEP especially in patients with corticospinal tract dysfunction. In order to circumvent this difficulty, some investigators have defined the silent period as the time interval from stimulus delivery to the return of voluntary activity.[68]

Most of the silent period is believed to be due to inhibitory mechanisms at the motor cortex, while spinal inhibitory mechanisms such as Renshaw inhibition are thought to contribute only to the first 50–60 ms of this suppression.[69–71] The silent period is most likely mediated by $GABA_B$ receptors.[72] Silent periods of abnormally short or long duration are observed in patients with various movement disorders.[26,27,49] Patients with amyotrophic lateral sclerosis often have a shortened duration of silent periods due to impairment of intracortical inhibition that can be reversed by antiglutamatergic drugs; these findings provide insights into the pathophysiology of this disease.[54,73] Classen and co-workers[74] investigated patients after acute stroke, who showed hemiparesis and a long duration of the silent period but normal central motor conduction time and MEP in the affected side. These patients had impaired movement initiation, inability to maintain a constant force, and impaired movement of individual fingers that resembled motor neglect. The silent period duration decreased with clinical improvement. This study suggests that among patients with hemiparetic stroke there is a subgroup whose motor disorders, involving features of motor neglect, are caused by exaggerated inhibitory mechanisms in the motor cortex rather than by a direct corticospinal disorder. The silent period in TMS might be useful in the assessment of pathophysiology and guide therapeutics of this and other motor syndromes.

Transcallosal conduction

TMS delivered to one motor cortex can suppress ongoing voluntary electromyographic activity in small hand muscles ipsilateral to the site of stimulation. This can be shown by applying a single suprathreshold TMS pulse to the motor cortex while a person maintains the intrinsic muscles of the ipsilateral hand contracted: an ipsilateral silent period can be recorded (figure 4). This period of inhibition begins 10–15 ms after the minimum corticospinal conduction time to the recorded hand muscle, and

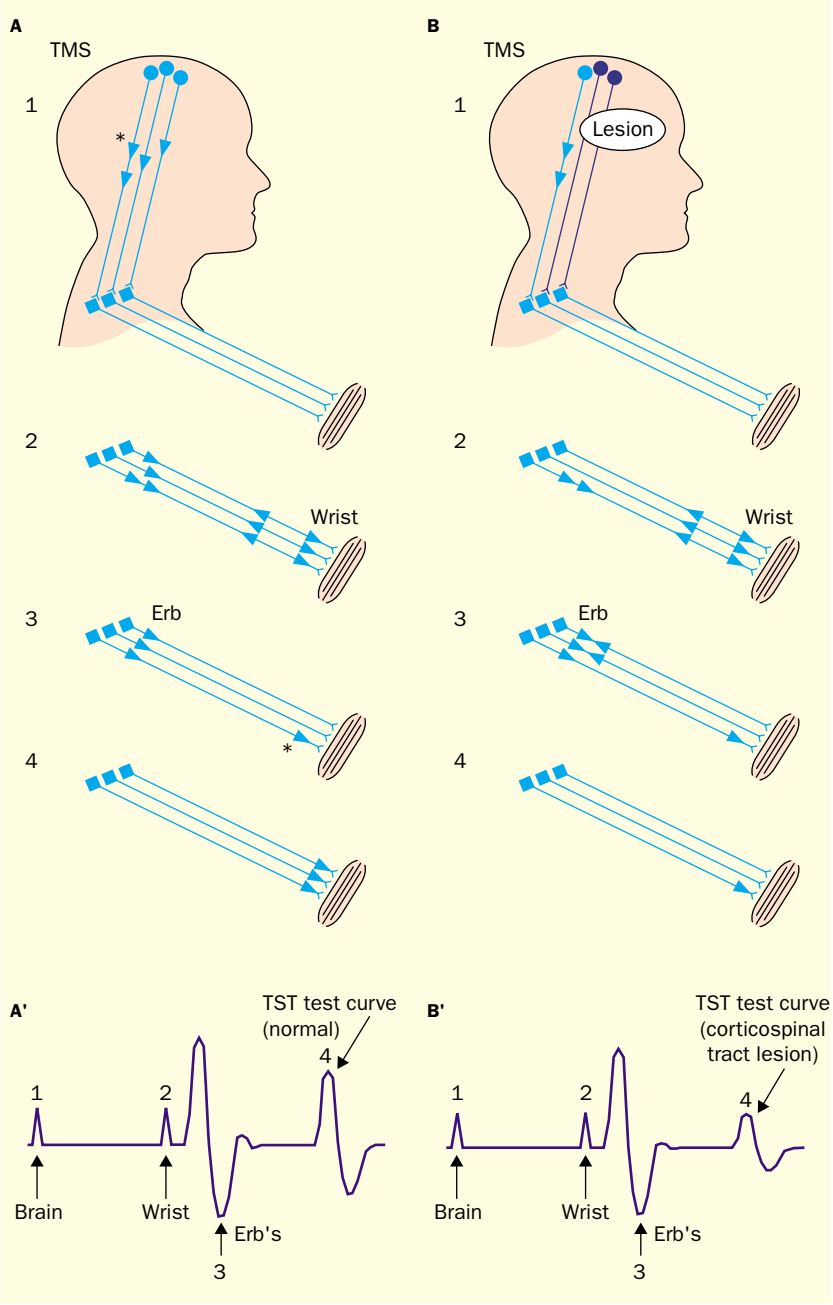

Figure 3. The principle of the triple stimulation technique (TST), consisting of a single pulse TMS to the motor cortex and peripheral nerve stimuli at Erb's point and the wrist. The size of response to the stimulus at Erb's point is studied (TST curve). In a healthy individual, maximum TMS excites all axons and desynchronisation occurs (A). 1: Maximum TMS is applied on the motor area and evokes descending volleys with various latencies, including multiple volleys (*). 2: after a delay, a supra-maximal stimulus is given at the wrist that evokes a first large response (orthodromic action potentials) and also an activation that travels towards the spinal cord (antidromic action potentials) and collides with and cancels descending action potentials. 3: the second discharge (*) on the axon is not cancelled and causes a small response. 4: after a delay, a maximal stimulus is applied at Erb's point and synchronised response from all axons excited initially by TMS is recorded as a second response. A': a possible TST result in a healthy individual. TST in a patient with a partial failure of the central conduction (B). 1: even maximum TMS cannot excite all axons. 2–4: due to the conduction failure, only a part of peripheral nerves are synchronised and the TST test curve is smaller than that of the TST control curve. B': a possible TST result in a patient.

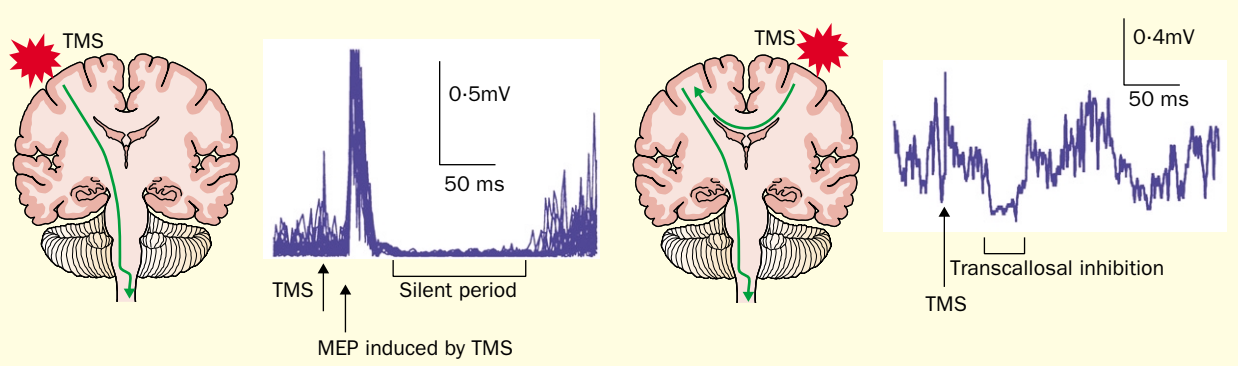

Figure 4. The effect of TMS on a motor area that represents a voluntarily contracted hand muscle. Responses are recorded from the left first dorsal interosseus muscle (FDI). Left: example of a silent period to TMS. Stimulation of the left motor cortex elicits MEPs in the contralateral (right) FDI, which is followed by a suppression of tonic voluntary electromyographic activity. Rectified consecutive 15 electromyographic responses are superimposed. The muscle contraction is kept with 20% of maximum voluntary force pressing a force transducer. The intensity of TMS is set at 130% of the motor threshold. Right: transcallosal inhibition. TMS of the ipsilateral (left) motor cortex inhibits tonically firing corticospinal neurons in the motor cortex of the unstimulated hemisphere and thus produces a transcallosal inhibition of tonic electromyographic activity in the ipsilateral FDI. The muscle contraction is kept with 50% of maximum voluntary force. The intensity of TMS is set at the maximum of the TMS machine. 20 consecutive rectified electromyographic responses are averaged.

has a duration of about 30 ms.[37] Inhibition is thought to be mediated via transcallosal pathways and to stem from the level of the motor cortex. In the patients with lesions in the corpus callosum, this transcallosal inhibition is either delayed or absent.[37,38] In multiple sclerosis, the involvement of the corpus callosum can be clinically undetectable, but is thought to be associated with poor prognostic value regarding cognitive functions.[75] This transcallosal technique might add valuable functional information to the highly detailed structural insights gained from MRI studies in patients with multiple sclerosis.[39,40] This TMS method can be associated with the paired-pulse TMS technique to investigate interhemispheric interactions further.

Paired-pulse TMS

The examination of intracortical inhibitory and facilitatory mechanisms

Inhibitory and facilitatory interactions in the cortex can be studied by combining a subthreshold conditioning stimulus with a suprathreshold test stimulus at different short (1–20 ms) interstimulus intervals through the same TMS coil. This method was first introduced for the study of the motor cortex (figure 5),[76] but can also be applied to non-motor areas.[77] The effects of the conditioning TMS on the size of a test MEP depend on the stimulus intensity and the interstimulus interval. Maximum inhibitory effects are found at short interstimulus intervals of 1–4 ms and conditioning stimuli of 60–80% of the resting motor threshold.[76,78] The maximum amount of this inhibition is commonly 20–40% of the test MEP. Facilitatory effects of the conditioning TMS pulse on the test MEP can be observed at intervals 7–20 ms.[76,79] The magnitude of this facilitation can be quite variable among individuals (from 120% to 300% of the test MEPs). The magnitude of the intracortical inhibition and facilitation vary depending on the amplitude of the test MEPs and the degree of contraction of the target muscle, a critical variable to control for in paired-pulse TMS studies. These phenomena of intracortical inhibition and facilitation are very similar for intrinsic hand, lower face, leg, and proximal arm muscles, indicating that these intracortical mechanisms are similar across different motor representations.[80,81] As measured by this technique, intracortical inhibition and facilitation are induced by separate mechanisms and their effects seem to originate in the motor cortex.[76,79,82]

This paired-pulse technique has been used to investigate the effects of CNS-active drugs on the human motor cortex.[52] In this context, paired-pulse TMS might be useful in selecting the best-suited medication for a given patient by matching the identified abnormality in a given disorder with the effects of different pharmaceutical agents. Such a neurophysiology-based approach to medication selection in epilepsy or psychosis would certainly be desirable, though systematic studies are needed and the procedure may ultimately prove too cumbersome to be clinically useful.[34,83]

Paired-pulse TMS has been used to study the pathophysiology of various neurological and psychiatric diseases.[26,27,49,84,85] These results are interesting but seem to be rather non-specific. For example, essentially the same abnormalities in the paired-pulse curve can be seen in dystonia and idiopathic Parkinson's disease.[26,27,49,50,85] Furthermore, disorders without clear motor-cortex pathology, such as schizophrenia, depression, or obsessive–compulsive disorder have been found to be associated with changes in the TMS paired-pulse curve,[86–88] hence raising further questions about the specificity of the findings. Nevertheless, longitudinal studies of the paired-pulse responses to TMS may well have prognostic significance for neurological and psychiatric diseases and should be done.[34,83]

The examination of interhemispheric interactions

Paired-pulse stimulation can also refer to the application of single stimuli to two different brain regions. For example, a first conditioning suprathreshold stimulus is given to one motor cortex and after a short interval (4–30 ms) a second,

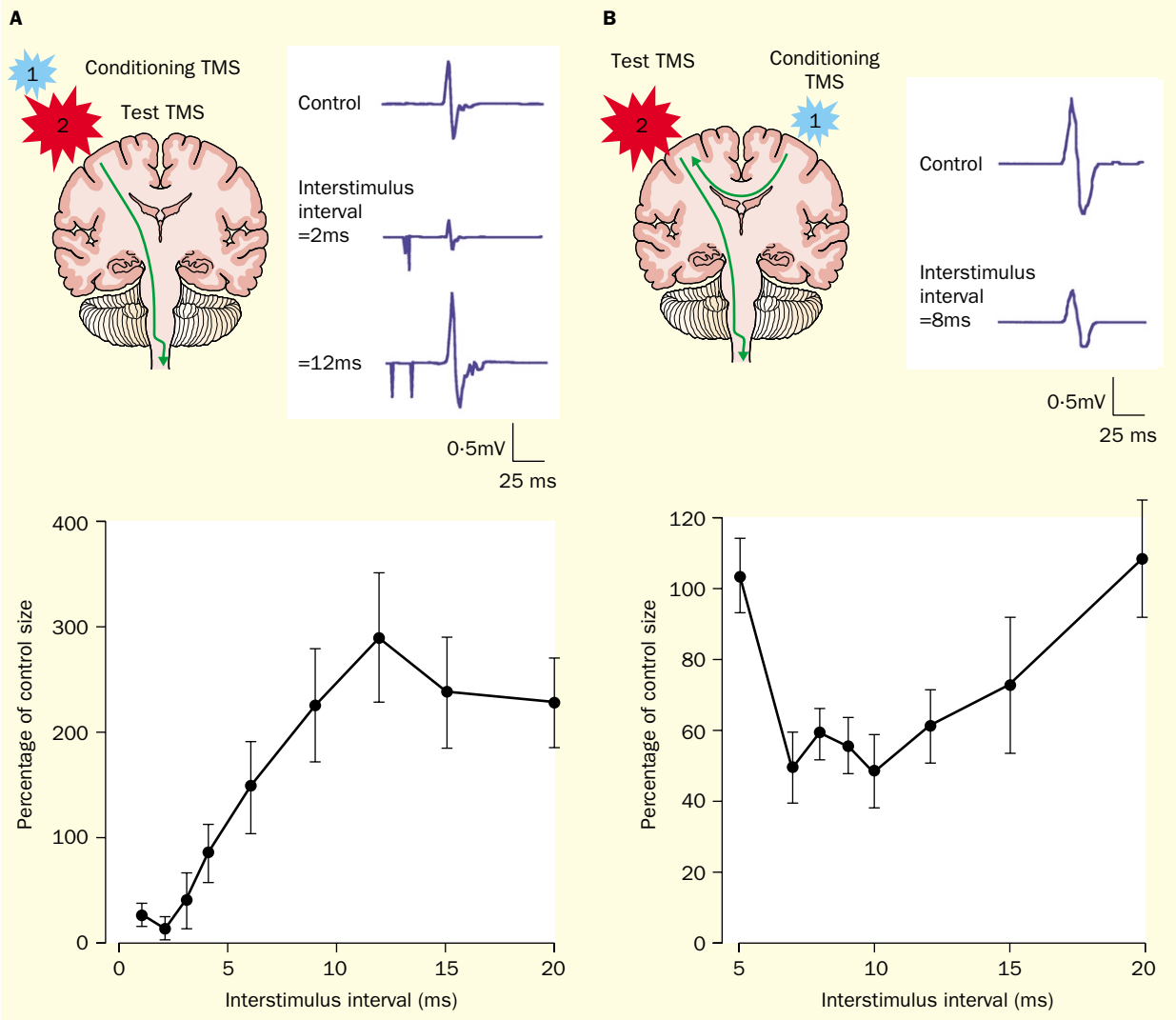

Figure 5. (A) The change of MEP sizes obtained by the paired conditioning-test-stimulus paradigm from the first dorsal interosseus (FDI) muscle. The intensity of conditioning TMS was set to 80% of resting motor threshold. The intensity of test TMS was adjusted to produce a control MEP of an average peak-to-peak amplitude of 1 mV when given alone. In the graph, the size of the MEPs is expressed as a percentage of the control unconditioned MEPs, and plotted against the interstimulus interval. Data are means of eight healthy individuals (mean age 31·6 years [SD 4·9]). Error bars indicate standard errors. Note that the conditioning stimulus inhibited the test MEP at short interstimulus intervals (1–4 ms) but facilitated it at longer intervals (6–20 ms). (B) Modulation of the MEP sizes induced in the FDI by TMS of the contralateral motor cortex as a consequence of a conditioning TMS pulse applied to the motor cortex of the opposite hemisphere (ipsilateral to the target FDI). The intensity of the conditioning TMS was set to 110% of the resting motor threshold (for induction of MEPs in the contralateral FDI) and the intensity of the test TMS was adjusted to produce a control MEP of an average peak-to-peak amplitude of 1 mV when given alone. In the graph the size of MEPs is expressed as a percentage of the control MEP by unconditioned TMS, and plotted against the interstimulus interval. Data are means of the same eight healthy people as in A. Note the significant inhibition at the interstimulus interval of 7–12 ms.

test, TMS pulse is applied to the other motor cortex in order to examine interhemispheric interactions and transcallosal conduction times. This paradigm was first introduced by Ferbert and co-workers[89] who showed that 7–15 ms after suprathreshold TMS of one motor cortex the cortical excitability of the opposite motor cortex is decreased (figure 5). This interhemispheric interaction is influenced by the intensity of the conditioning TMS: the stronger the conditioning TMS the greater and longer the induced interhemispheric inhibition. Right-handed people have more pronounced interhemispheric influence of the right, non-dominant side by the dominant side than in the opposite direction.[90] As expected from animal experiments, low intensity TMS can be used to detect interhemispheric pathways with stimuli 4–5 ms apart in slightly contracted hand muscles.[91]

This methodology allows the investigation of interhemispheric interactions in motor control and movement disorders. Patients with cortical myoclonus show no such interactions, which indicates affected transcallosal or cortical inhibitory interneurons.[92] Patients with mirror movements or those recovering from a stroke are likely to show changes in these interhemispheric influences.[93,94] Future studies might establish this paired-pulse method as a clinically useful

diagnostic tool to elucidate mechanisms of pathological interhemispheric and intracortical interactions in neurological and psychiatric diseases. Certainly, this TMS methodology provides a unique opportunity to expand our understanding of the role of disconnection syndromes in cognition and disease.

TMS for neurosurgery

TMS can be used in the preoperative assessment of specific brain areas and for intraoperative monitoring of corticospinal motor tract function to optimise surgical procedures. During presurgical planning, it is sometimes necessary, in order to minimise the risk of post-surgical deficits, to identify the language dominant hemisphere, localise the language areas, or motor area that might have been shifted owing to compression by intracranial or intracerebral lesions. Functional imaging (eg, MRI) might be helpful in this regard. However, functional neuroimaging can only provide insight into the brain areas associated with a given behaviour, failing to establish a causal relation between brain activity and behaviour. In order to bridge the gap between association and causality it is necessary to disrupt the activity and assess the effect on behaviour. Functional MRI cannot tell the neurosurgeon that lesioning a given brain region, whether it shows activation during a task or not, will cause a post-surgical deficit. The combination of functional MRI with TMS can provide such insight.[17,95–97]

High frequency repetitive TMS (rTMS) of the dominant hemisphere, but not the non-dominant one, can induce a speech arrest and localise speech-related cortices.[98,99] Furthermore, Tokimura and colleagues[100] have reported an even less invasive way to identify the dominant hemisphere with single-pulse TMS to measure the increase in motor cortical excitability of the dominant (but not of the non-dominant) hemisphere during language tasks. The correlation of these TMS results with those of the intracarotid amobarbital (Wada) test is high but not satisfactory for a presurgical assessment.[98,99] Prospective clinical trials that relate the results of TMS with the intraoperative or postoperative findings are needed to establish the usefulness of the presurgical assessment of the language-dominant hemisphere by TMS.

Intraoperative monitoring of motor tract function during spinal or cerebral surgery is important to avoid the rare but devastating neurological sequelae of spinal injury. Monitoring of the integrity of the central motor pathways during surgery is therefore an appealing application of TMS. Recording of somatosensory evoked potentials alone is not entirely satisfying, because damage to the anterior and lateral cord can cause paralysis without affecting the posterior columns and hence without change in the somatosensory evoked potentials. Such false negative results have been found,[101] which highlights the importance of monitoring both descending and afferent pathways. Although intraoperative MEP recording can fail with inhaled anaesthetics,[102] development of intravenous anaesthetics (eg, propofol, remifentanil) has improved intraoperative monitoring of MEPs.[103] Intravenous anaesthetics such as propofol seem to suppress indirect waves at the cortical level, but high frequency repetitive stimulation can overcome this effect. Inhaled anaesthetics seem to have an additional suppressive effect on direct waves[104] and are not suitable for intraoperative monitoring. Regardless, during the surgical procedures in the vicinity of the motor cortex, TMS offers no real advantage over direct electric stimulation, which might be easier to implement in the operating room. However, for the surgery of spine or brainstem, or for surgical interventions with spinal anaesthesia, TMS may be advantageous because it is less painful and can be more focal than transcranial electrical stimulation.

Repetitive TMS

The technique

A train of TMS pulses of the same intensity applied to a single brain area at a given frequency that can range from one stimulus per second to 20 or more is known as rTMS. The higher the stimulation frequency and intensity, the greater is the disruption of cortical function during the train of stimulation. However, after such immediate effects during the TMS train itself, a train of repetitive stimulation can also induce a modulation of cortical excitability. This effect may range from inhibition to facilitation, depending on the stimulation variables (particularly frequency of stimulation).[105–107] Lower frequencies of rTMS, in the 1 Hz range, can suppress excitability of the motor cortex,[108] while 20 Hz stimulation trains seem to lead to a temporary increase in cortical excitability.[109,110] While these effects vary among individuals,[109,111] the effect of low frequency rTMS is robust and long lasting[108,109] and can be applied to the motor cortex and to other cortical regions to study brain–behaviour relations.

Several studies in human beings that combine rTMS and functional neuroimaging techniques (eg, MRI and PET) have detected suppressed or increased cerebral blood flow and metabolism in the stimulated area after slow (1 Hz) or rapid (10–20 Hz) rTMS of the motor cortex, respectively.[107,112,113] Similar phenomena have been observed after TMS to other cortical areas, such as frontal eye field and dorsolateral prefrontal cortex.[114,115] However, even when TMS is delivered at low intensity (below the motor threshold intensity), spinal reafferences accounting for or contributing to the detected neuroimaging results cannot be ruled out. Nevertheless, the combination of TMS and neuroimaging can be most helpful in the investigation of functional connectivity between regions in the living human brain.[113,114,116] Furthermore, the combination of rTMS with tracer PET[117] or magnetic resonance spectroscopy may become a novel tool to investigate neurochemical functional anatomy in health and disease.

The mechanisms of the modulation of cortical excitability beyond the duration of the rTMS train are still unclear. Long-term potentiation[118] and depression[119] of cortical synapses or closely related neuronal mechanisms have been suggested as possible mechanisms to explain the effect of high and low-frequency rTMS, respectively. Animal studies suggest that modulation of neurotransmitters[120,121] and gene induction[122,123] may contribute to these long-lasting modulatory effects of rTMS. Further work in animal models with appropriately sized TMS coils is needed to shed light on this issue.

Therapeutic use

The lasting modulation of cortical activity by rTMS is not limited to motor cortical areas. There is also evidence that these long-lasting effects of rTMS can be induced in areas outside the motor cortex and be associated with measurable behavioural effects, including visual,[124] prefrontal,[125] parietal cortex,[126] as well as the cerebellum.[127] This finding raises the possibility of therapeutic applications of rTMS to "normalise" pathologically decreased or increased levels of cortical activity. Several studies of various neurological disorders are providing tantalising results on such uses of rTMS. However, even with such favourable results, there might not be a causal link between improvement and the effect of TMS. More insights into the physiological basis for the behavioural effects of this technique are needed. In addition, to establish a clinical therapeutic indication for rTMS, well-controlled multicentre randomised clinical trials with high numbers of patients are required.

Treatment of depression is the most thoroughly studied of the potential clinical applications of rTMS. Lasting beneficial effects have been seen in about 40% of patients with medication-resistant depression in recent studies.[128–134] Both high frequency repetitive TMS of the left dorsolateral prefrontal cortex and low frequency stimulation of the right side can improve depression. Kimbrell and colleagues[115] suggested that patients with decreased cerebral metabolism might respond better to high frequency and those with hypermetabolism may respond better to low frequency stimulation, which is in line with the frequency-dependent effects of rTMS on the motor cortical excitability.

Pascual-Leone and co-workers[135] first reported that in five patients with Parkinson's disease submotor-threshold rTMS at high frequency (5 Hz) to the motor cortex improved contralateral hand function. There are two rationales for trials of this method in Parkinson's disease: first, increasing cortical excitability to thalamocortical drive, which is believed to be lacking in this disease; and second, modifying catecholamine metabolism subcortically through cortical stimulation.[136] The mild benefits were reproduced by the other groups[137,138] and Strafella and colleagues[117] recently have shown that rTMS of the prefrontal cortex can increase dopamine in the caudate nucleus. However, other careful and systematic studies have not shown any favourable effects.[139,140] These contradictory results for rTMS in patients with Parkinson's disease draw attention to the difficulty of proving a clinical therapeutic effect, the likely variability of TMS effects across individuals, and the importance not to extrapolate from an acute, symptomatic change in very few patients to a claim of therapeutic applicability.

After physiological studies of task-specific dystonia suggested hyperexcitability of the motor cortex or a failure of intracortical inhibition,[28] rTMS of the motor cortex at 1 Hz has been used to treat patients with writer's cramp.[141] The improvement of deficient intracortical inhibition and handwriting lasted at the most 3 h after application of a 30 min train of TMS but resulted in clinical benefits in only 2 of 16 patients studied. In tic disorder, a similarly abnormal increase of cortical excitability is reported,[142] and 1 Hz rTMS of the motor cortex can reduce the frequency of tics.[143] These effects are transient, but the data support the concept of impaired inhibitory mechanisms in the motor cortex.

Several other studies have tried to use low-frequency rTMS to treat other diseases, for example intractable seizures[45,144] and cortical myoclonus,[145] and showed successful reduction in the frequency of seizures or abnormal movements, but in very few patients. Similar logic might be applicable to spasticity, intractable neurogenic pain, or schizophrenia, where suppression of abnormally increased cortical excitability might achieve desirable symptomatic relief.

Outcome after stroke may be favourably influenced by rTMS suppressing maladaptive cortical plasticity and improving adaptive cortical activity to promote neurorehabilitation. Functional imaging studies after stroke show increased activity in undamaged brain areas,[146,147] but the role of these areas is controversial.[148] Some activation in the uninjured brain could reflect adaptive cortical reorganisation that promotes functional recovery, but some changes may be maladaptive and generate the emergence of behaviours, suppression of which would improve functional outcome. The symptoms after a brain damage are as much due to the damage as to the changes in activity across the undamaged brain. Contralesional neglect after stroke is not due to the lesion itself but primarily due to the hyperactivity of the intact hemisphere, and 1 Hz rTMS of the unaffected parietal lobe to suppress excitability of the intact hemisphere can improve contralesional visuospatial neglect after stroke.[149] Naeser and co-workers[150] have shown that patients with Broca's aphasia may improve their naming ability after 1 Hz rTMS of the right Brodmann's area 45 that is supposed to be overactivated in patients with unrecovered, non-fluent aphasia. These observations are transient and it is premature to propose them as realistic therapeutic applications. Nevertheless, rTMS of the region of interest detected in functional images could highlight the property of plastic changes of the cortical circuitry and hint at future novel clinical interventions.

Conclusion

TMS was introduced nearly 20 years ago and has developed as a sophisticated tool for neuroscience research. TMS is a non-invasive and effective methodology with potential diagnostic and therapeutic uses. Studies to date have not provided enough data to establish the clinical indication for a systematic application of TMS as a diagnostic or therapeutic tool in any neurological or psychiatric disease. Nevertheless, the ability of TMS to measure and modify cortical activity offers exciting capabilities that warrant carefully designed clinical trials. Combined with neurophysiological studies in animals and human beings that expand our understanding on the mechanisms of action of TMS, future work promises to provide valuable advances in our understanding of the pathophysiology of a wide range of neuropsychiatric conditions, generate widely applicable diagnostic tools for clinical neurophysiology, and perhaps establish neuromodulation as a viable therapeutic option in neurology, neurorehabilitation, and psychiatry.

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Conflict of interest

We have no conflicts of interest.

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Search strategy and selection criteria

Data for this review were identified by searches of Medline and the references from relevant articles; numerous articles were also identified through searches of our files. The search terms "transcranial magnetic stimulation" and "magnetic stimulation" were used in addition to several neurological diseases and those of internationally renowned experts in the use of TMS. Abstracts and reports from meetings were included only when no full paper has been published on the topic and the findings were deemed to be of critical importance. Papers published in English were preferentially reviewed.

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