

Cerebral function revealed by transcranial magnetic stimulation

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Abstract

Although transcranial magnetic stimulation (TMS) has been introduced only recently, it is safe and provides a painless, inexpensive noninvasive method for the evaluation of brain function. Determining central motor conduction time (CMCT) permits assessment of the corticospinal pathways. Mapping the central representation of muscles provides a method for investigating the cortical reorganization that follows training, amputation and injury to the central nervous system. Such studies of human plasticity may have important implications for neurorehabilitation. TMS also provides a method whereby cortical excitability can be noninvasively evaluated, which is likely to have important implications in the study of epilepsy, movement disorders and related conditions. TMS is useful in tracking the flow of information from one brain region to another and in investigations of cognition and functional localization, thereby complementing information obtained using functional imaging techniques, which have superior spatial but inferior temporal resolution. Finally, TMS is currently being investigated as a method for establishing cerebral dominance and as a therapeutic tool in the treatment of depression. Investigations for treatment of other neurologic and psychiatric conditions are likely to be undertaken. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Gualiterotti and Patterson (1954) were the first to stimulate the unexposed motor cortex of humans with repetitive electrical shocks. The stimulation was too painful for the procedure to be used experimentally or clinically. Subsequently, Merton and Morton (1980) applied brief condenser discharges of about 2000 V to scalp bipolar leads for transcutaneous, transcranial stimulation of the motor cortex in normal human subjects. The electrical stimuli produced impulses preferentially beneath the anode rather than the cathode which excites peripheral nerve. Limb movements were elicited and compound motor action potentials (CMAPs) were recorded from limb muscles. This technique produced considerable discomfort and strong contractions of jaw muscles. Efforts were therefore made to improve the technique so that weaker stimuli might be used. Merton et al. (1982) discovered that contraction of the limb

muscles being recorded facilitated the CMAPs and that smaller stimuli produced larger responses during voluntary contraction. They also found that the effective stimulus intensity can be reduced by using larger stimulating electrodes. Subsequently, Hassan et al. (1985), using predominantly monopolar stimulating electrode configurations, found that electrical stimuli of about the same magnitude as those used in peripheral nerve conduction studies are effective transcranially.

Transcranial magnetic stimulation (TMS) was introduced by Barker et al. (1985). In this technique, a large current pulse is discharged through a copper coil placed tangentially on the scalp and centered on the vertex. This results in a strong time-varying magnetic field, which in turn induces an electrical current in the brain with the maximum field under the coil windings. The direction of the induced current is opposite to that in the coil. Because the magnetic field traverses the skull essentially without diminution, a large current flow in extra cerebral tissues is not required to induce an adequate stimulus to the brain; therefore, stimulation is

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painless. Consequently, when single stimuli are applied, the perceived local sensation is that of a touch or tap to the scalp.

2. Stimulating technique

With TMS, a magnetic coil (MC) is used as a vehicle to painlessly induce an electrical current in the underlying volume conductor (brain). It is the current and not the magnetic field that excites neural tissue. A typical stimulator used for TMS consists of an energy storage capacitor with a low series resistance that is discharged into a stimulation coil by a solid-state switch. In order to produce the high-intensity, rapidly changing magnetic field needed to induce adequate current to stimulate excitable tissue, a high peak current (in the kiloampere range) is rapidly delivered to the coil which initially was placed tangentially on the scalp. The changing magnetic field produced by the current in the coil induces a current in the brain that is proportional to the rate of change of current in the coil. The duration of the induced current is short, typically 0.1 ms and it is opposite in direction to the current in the coil. The peak magnetic field at the center of commercially available MC's is 1.5–2.5 Tesla and depends on coil size and geometry (Barker, 1991; Jalinous, 1991).

Changes in MC size, shape, and geometry affect the localization and depth of stimulation (Cadwell, 1991). The geometry of the coil windings determine the density of the magnetic flux. The induced voltage increases linearly with the total flux. Nonuniformity of the flux will increase the power necessary to produce the magnetic field more than it increases the induced voltage; therefore, MC's with uniform flux are more efficient than those with a concentrated flux. However, greater localization of stimulation occurs if the windings are concentrated near the edge of the coil. Increasing MC size also reduces flux density. Larger MCs are more efficient because greater total flux can be generated for a given amount of power. Greater penetration of tissue is also possible with a larger coil because the flux does not decrease as rapidly as with a small coil. Smaller MCs produce more focal stimulation because flux is more restricted. However, smaller MCs have higher mechanical pressures, and the heat generated is confined to a smaller volume, so temperature rise in the coil may be a problem. Also, with smaller coils, induced current in the skin is greater than with large coils; this can result in greater stimulation of pain receptors.

In order to improve the focality of stimulation over the cortex, a departure is needed from placing a round coil on top of the head. Movements predominantly of individual digits were obtained by a tilted orientation, with only a portion of the coil contacting the scalp, i.e. 'edge stimulation' (Amassian et al., 1987a). A much

more convenient arrangement is the 'figure-eight' or 'butterfly' coil (Ueno et al., 1988; Amassian et al., 1989a; Barker, 1991; Cadwell, 1991). It consists of two adjacent coils joined together with the current running in opposite directions in each coil. Therefore, currents are in the same direction at the junction region. This results in induced currents that are two times greater under the junction than under the outside coils, which makes excitation most likely to occur under the junction. Furthermore, this coil can be laid flat on the scalp (cf edge stimulation).

Most commercially available stimulators are limited to slow rates of stimulation of about 0.3–1 Hz, mainly because of coil heating. Recently, rapid-rate stimulators, which are capable of discharging trains of stimuli at repetition rates of up to 60 Hz, have been introduced. The safety of these stimulators is currently under investigation (Pascual-Leone et al., 1993).

3. Safety

Extensive use of single pulse TMS as a clinical tool in Europe indicates that it is a safe procedure. Theoretical risks that have been considered include direct electrical, thermal, or magnetic injury to the brain, induction of seizures and kindling, hormonal abnormalities, changes in higher cortical function, and hearing impairment (Agnew and McCreery, 1987; Barker et al., 1988; Bridgers and Delaney, 1989; Bridgers, 1991; Counter et al., 1990; Krain et al., 1990; Levy et al., 1990a; Cracco et al., 1993; Chokroverty et al., 1995).

The magnetic, electrical, and thermal energy levels that occur in the brain during TMS are within safe limits based on experimental data and other accepted clinical procedures (Agnew and McCreery, 1987; Barker et al., 1988). Studies involving EEG, serum prolactin, ACTH, and cortisol levels have not shown any changes related to TMS (Cohen and Hallett, 1987; Krain et al., 1990; Levy et al., 1990a; Bridgers, 1991), and to date, short- or long-term cognitive changes have not been observed (Bridgers and Delaney, 1989).

Kindling refers to the application of subthreshold electrical stimuli to the brains of animals to produce independent seizure foci. In experimental animals it has been shown that the risk of neuronal kindling is linked to the frequency of stimulation (Goddard et al., 1969). Such a risk is nearly nil with stimulus repetition rates below 10 Hz, a frequency that is considerably greater than that used in routine clinical studies using single stimuli.

There are only three reports of induced seizures with single pulse TMS; one patient had an old stroke, and the two other patients had epilepsy (Homberg and Netz, 1989; Hufnagel et al., 1990; Tassinari et al., 1990). However, rapid-rate, high-intensity TMS was

recently reported to cause a focal and secondarily generalized seizure in a normal subject with no definitive risk factors other than a family history of epilepsy (Pascual-Leone et al., 1993). Seizures have occurred in several other normal subjects with repetitive stimulation. There is therefore definite risk for seizures with repetitive stimulation and great caution must be exercised.

Counter et al. (1990) drew attention to another possible hazard of TMS. During stimulation, the MC produces a brief, high-intensity click. This was shown to cause permanent threshold changes in the unprotected ears of experimental animals after only 50 MC discharges. Pascual-Leone et al. (1992) found no hearing loss in human subjects exposed to multiple sessions of single-pulse TMS. However, rapid-rate (1–25 Hz) TMS resulted in temporary threshold changes in several subjects. These authors recommended that individuals exposed to TMS at frequencies of 1 Hz or greater should wear earplugs (Pascual-Leone et al., 1993).

Because skull fractures, or craniotomy sites could represent potential hazards, patients with skull defects are usually excluded from study (Agnew and McCreery, 1987; King and Chiappa, 1990). Metal objects may intensify induced currents or be subjected to significant forces, so patients with pacemakers or other implanted devices, or metal in the head or brain, should not be tested. Although patients with seizures and children less than 18 years have been tested without problems, they are usually excluded from study in the United States.

4. Conduction in central motor pathways

The most common excitatory phenomenon elicited by TMS is the CMAP and associated limb movement following contralateral motor cortex stimulation. The mechanism underlying this has been investigated. Single electrical stimuli delivered to the surface of the motor cortex in anesthetized monkeys elicits a series of positive waves in extracellular recordings obtained from the corticospinal tract. These potentials have a period of 1.0–1.5 ms and last 5–10 ms (Fig. 1). The first of these waves was termed the direct or D wave, and the subsequent waves indirect or I waves (Patton and Amassian, 1954, 1960; Amassian et al., 1987b) (Fig. 1). The latency of the D wave is too short to allow time for an interposed synapse. The I waves require intact gray matter, whereas D waves can be obtained by stimulating white matter after cortex is ablated. Based on this and on the effects of anesthesia, asphyxia, and high-frequency cortical stimulation, it was proposed that the D wave is the result of direct excitation of corticospinal tract neurons at the axon hillock or the first or second node and that I waves reflect transsynaptic excitation of corticospinal tract neurons via cortico–cortical path-

ways in which one or more synapses are involved. The lack of temporal dispersion of D and I waves in extracellular corticospinal tract recordings from ipsilateral medulla and contralateral cervical spinal cord led to the conclusion that both D and I waves arise in fast-conducting large-diameter corticospinal tract axons that have conduction velocities of 60 to 70 m/s. Temporal and spatial summation of D and I waves is required to depolarize spinal motor neurons in the anesthetized animal (Brookhart, 1952). However, because voluntary contraction facilitates the CMAPs in the muscles being activated by TMS, i.e. decreases their latency by several ms and increases their amplitude, this suggests that with facilitation, D waves alone may be sufficient to discharge anterior horn cells.

When the coil is tangentially oriented and centered on the vertex, TMS of motor cortex at low to moderate intensity produces CMAPs in arm and hand muscles with latencies 1–2 ms longer than those evoked by electrical stimulation (Hess et al., 1987). These latency differences are probably related to differences in the direction of current flow induced in the brain by these two methods of stimulation. The current induced by an MC placed tangentially over the scalp and centered at the vertex tends to flow parallel to the surface with little or no perpendicular current flow (Roth et al., 1991). In contrast, with electrical stimulation, there is both vertical and horizontal current flow. The current induced by a MC centered at the vertex would, therefore, predominantly excite horizontally oriented cortical elements

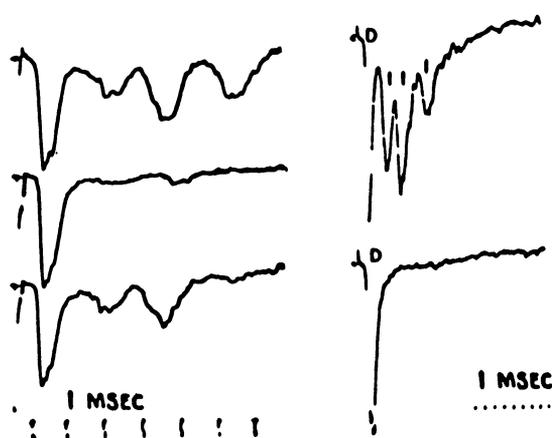


Fig. 1. Effects of depression (left) and ablation (right) of motor cortex on corticospinal tract responses following stimulation of motor cortex in the monkey. Dial anesthesia. Top records show normal direct (D) and periodic, indirect (I) waves after a brief stimulus. Left, middle, and bottom records show the effect of temporary depression, followed by recovery 14 min later. Right bottom record was obtained with stimulation of exposed white matter after ablation of the motor cortex. Left records were taken from the ipsilateral medullary pyramid; right records were taken from the contralateral lateral column at C-1 to C-2. (Left records from Patton and Amassian (1954), with permission; right records from Patton and Amassian (1960), with permission.)

such as interneurons and cortico–cortical fibers and, thus, would preferentially excite corticospinal tract neurons transsynaptically, resulting in I waves. Conversely, electrical stimulation, with its horizontal and vertical current flow, would be expected to elicit both D and I waves. Therefore, the minimal latency difference in arm muscle responses between electrical and vertex centered TMS probably represents the interval between the D and the first I wave (Day et al., 1989). However, when the coil is oriented laterally-sagittally over arm area, magnetic and electrical stimulation elicit CMAPs with identical latencies (Amassian et al., 1987a, 1990). Thus, the orientation of the coil crucially determines which cortical elements are initially activated.

Abnormalities of conduction in central motor pathways in a variety of neurologic disorders have been demonstrated by studying central motor conduction time (CMCT). CMCT is defined as the latency difference between the CMAPs to scalp (motor cortex) and spine (motor root) stimulation. It is usually less than 7 and 15 ms for upper and lower limb stimulation, respectively. Although no abnormality of CMCT is specific for a particular disease process, marked prolongation of CMCT suggests demyelination of central motor pathways; low-amplitude responses with little delay or absence of responses is more suggestive of loss of neurons or axons. Typically, in multiple sclerosis and also in cervical spondylitic myelopathy, CMCT is prolonged with dispersed and attenuated responses, whereas in amyotrophic lateral sclerosis responses are of low amplitude with only mild delays. In multiple sclerosis CMCT determinations only occasionally identify clinically silent lesions and in other conditions the sensitivity of this technique is not high which limits its clinical application.

5. Brain connectivities

TMS has been used to study conduction through the corpus callosum and the cerebellothalamo frontal pathway. Transcallosal responses have been recorded from the posterior frontal scalp following TMS over the contralateral homologous cortex (Cracco et al., 1989). These evoked responses are initially positive and have onset latencies of 8.8–12.2 ms (Fig. 2). These latencies are consistent with the differences in EMG latencies from the two limbs in patients with stimulus-sensitive myoclonus, which presumably reflects transcallosal conduction time (Shibasaki et al., 1978; Wilkins et al., 1984). Transcallosal responses are thought to be mediated by direct and indirect activation of callosal projection neurons primarily located in

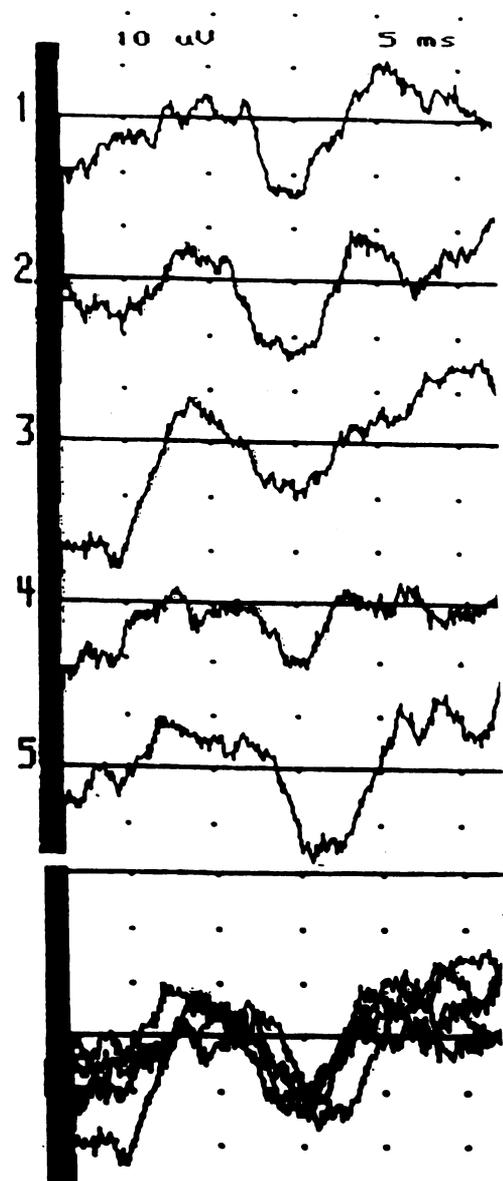


Fig. 2. Five successive transcallosal responses to TMS. Responses are superimposed in the bottom trace. Positivity at the recording electrode is indicated by a downward deflection. Stimulus artifact is followed by the transcallosal response. (From Cracco et al. (1989) with permission.)

layer IIIb and to arise from synaptic activity in the recipient cortex.

Focal TMS over the posterior basioccipital area has been used to elicit cerebellofrontal cortical responses from central and frontal scalp regions (Amassian et al., 1992). These responses have latencies of 8.8–13.8 ms, last 17.4–29 ms, and have a maximum amplitude of 14 μ V. They are predominantly surface-positive and contralateral to the side of cerebellar stimulation. This response is thought to reflect either dysfacilitation through excitation of Purkinje cells or feedforward facilitation through transsynaptic or antidromic excitation of dentate neurons.

6. Sensory functions of frontal lobe

Somatosensory phenomena can be elicited following single TMS of the frontal lobe. In contrast, a train of repetitive electrical stimuli of the exposed human parietal lobe is required to elicit sensation (Libet et al., 1964). Frontal lobe TMS produces a sensation of movement in the fingers after the forearm and hand have been anesthetized and paralyzed by an ischemic nerve block (Amassian et al., 1989a). The sensation is brief and has a short latency. Increasing the stimulus strength often increases the intensity of the sensation, and slight shifts in the position of the MC over frontal cortex can shift the projected sensation from one digit to another. In a minority of normal subjects, unambiguous, localized paresthesias have been reported following a single TMS delivered to frontal cortex (Amassian et al., 1991a). The paresthesias occur in the contralateral fingers and feel like electrical stimulation of the skin. Changing the site of stimulation results in changes in the site of the projected sensation. The generation of both paresthesias and sense of movement by frontal cortex TMS may reflect projected activity from frontal cortex to sensory and perceptual systems, possibly through connections with the thalamic intralaminar system and may be related to the will to make a movement (Amassian et al., 1995).

7. Excitability of motor cortex

The excitability of motor cortex can be studied using TMS by investigating motor threshold to single magnetic pulses, or to double pulse stimulation (intracortical excitability) and, the duration of the silent period. Motor threshold intensity, expressed as a percentage of maximum stimulator output, may be defined as the highest stimulus intensity that fails to produce a CMAP of more than 50 μ V in the target muscle in five or more successive trials. A measure of 'intracortical excitability' is obtained by delivering paired stimuli. The first or conditioning shock is subthreshold (80% of motor threshold) and the test shock is suprathreshold (120% of motor threshold). Such a conditioning stimulus has no effect on the size of the H reflex so that any effect of the conditioning shock on the test shock probably arises at a cortical level (Kujirai et al., 1993). In normal subjects, the conditioning stimulus produces an inhibition of the test response at short interstimulus intervals (1–5 ms) and a facilitation at longer intervals (7–30 ms) (Fig. 3).

During voluntary muscle contraction, a silent period, i.e. an interruption in EMG activity, follows the CMAP induced either by electrical stimulation (Calancie et al., 1987) or by TMS of the contralateral motor cortex (Amassian et al., 1990; Fuhr et al., 1991; Cantello et al.,

1992). Its duration is variable, sometimes exceeding 200 ms, and it is usually terminated by a recurrence of EMG activity (Fig. 4). Its duration is dependent on stimulus intensity, degree of muscle contraction, and site of stimulation over frontal cortex. Therefore, these variables must be considered in investigations of the silent period. The initial portion of the silent period reflects inhibition primarily at a spinal cord level through multiple mechanisms including Renshaw and Golgi tendon organ activation. The later portion of the silent period reflects primarily cortical inhibition (Fuhr et al., 1991; Uncini et al., 1993; Wilson et al., 1993). The cortical component reflects inhibitory processes within the cortical network causing a reduction in the excitatory corticospinal tract output and it does not arise from a direct inhibitory output. The silent period is short in Parkinson's disease, long in Huntington's disease, lengthened by levodopa and shortened by neuroleptics (Ziemann et al., 1996a). These observations and the finding that dopamine agonists increase intracortical inhibition (Ziemann et al., 1996a) support the notion that the basal ganglia dopaminergic system plays an important role in producing cortical inhibition.

The motor threshold to single magnetic pulses is lower in untreated patients with idiopathic generalized epilepsy than in healthy control subjects (Reutens and Berkovic, 1992; Reutens et al., 1993) and intracortical inhibition observed with two pulses is impaired (Fuhr et al., 1991). Patients with cortical myoclonus (Brown et al., 1996) and juvenile myoclonic epilepsy (Caramia et al., 1996) also have reduced intracortical inhibition. In focal epilepsy, only the affected hemisphere shows an increased cortical excitability (Fong et al., 1993). Therefore, it may be possible to characterize disturbed cortical excitability in epileptic patients on the basis of altered threshold to single pulses or intracortical excitability measured with two pulses.

Ziemann et al. (1996b) studied the effect of a single oral dose of antiepileptic drugs on the excitability of the motor system in healthy volunteers using TMS (Fig. 3). Vigabatrin and Baclofen, which increase the action of the inhibitory neurotransmitter GABA, reduced intracortical excitability (enhanced inhibition with TMS paired pulse stimulation at ISI's of 1–5 ms and suppressed intracortical facilitation at ISI's of 7–30 ms) but had no effect on motor threshold. Gabapentin, whose mechanism of action is uncertain, showed a similar effect. Conversely, carbamazepine, lamotrigine and losigamone, which are sodium and calcium channel blockers and are not thought to have significant neurotransmitter properties, elevated motor threshold but did not change intracortical excitability. The cortical silent period was lengthened by gabapentin and carbamazepine. This suggests that changes in intracortical excitability are caused by GABA controlled intraneuronal circuits in the motor cortex while changes in

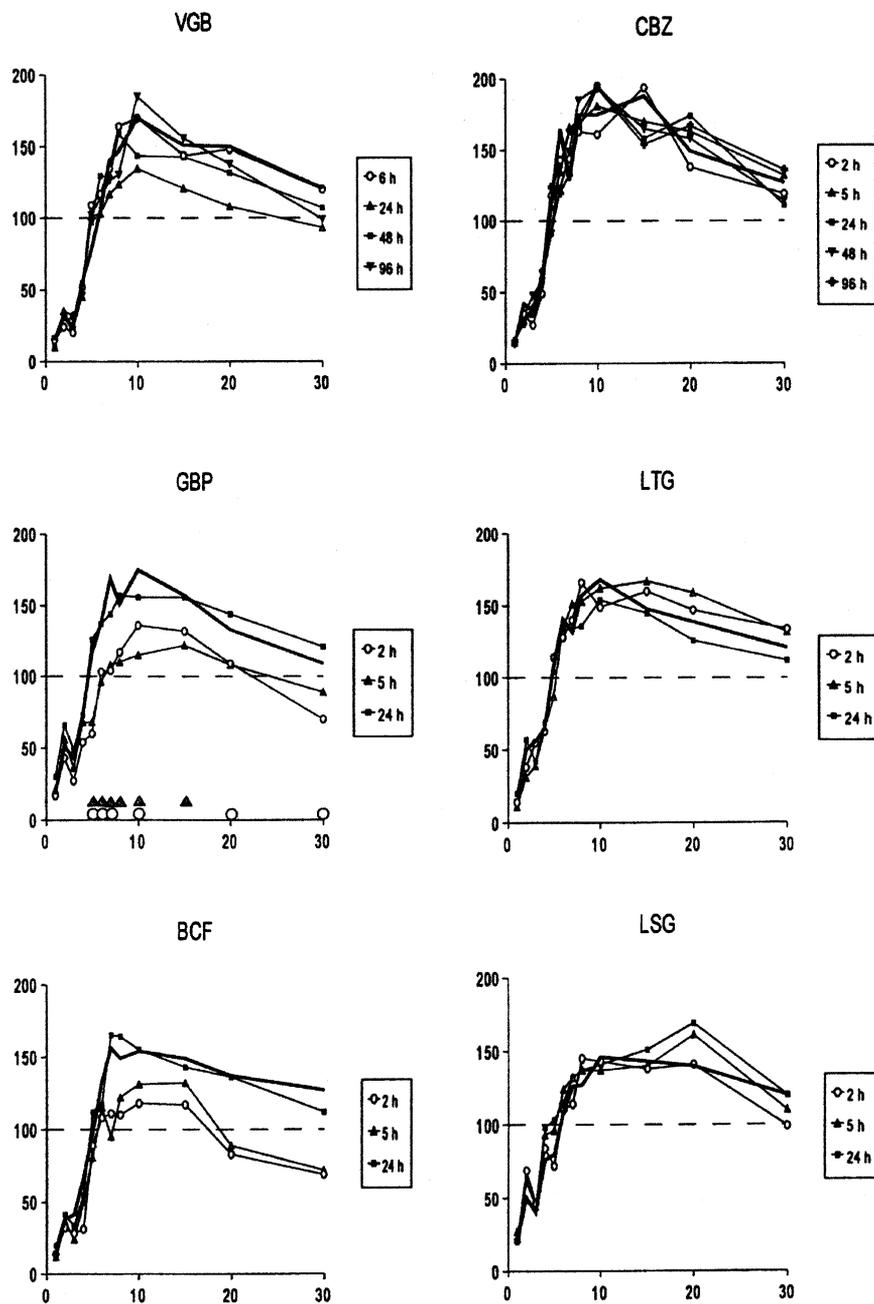


Fig. 3. Effects of antiepileptic drugs on mean intracortical excitability as obtained by the paired conditioning-test-stimulus paradigm. In each of the diagrams, the interstimulus interval (ISI) (in ms) between the subthreshold conditioning and the suprathreshold test stimulus is given on the x axis. The change in the size of the unconditioned control response by the conditioning shock is expressed on the y axis as a percentage of the unconditioned mean. Baseline curves are indicated by the thick lines. All other curves relate to measurements done at various times after drug intake. The symbols along the x axis indicate significant drug effects at the corresponding measurements and ISIs. VGB, vigabatrin; GBP, gabapentin; BCF, baclofen; CBZ, carbamazepine; LTG, lamotrigine; LSG, losigamone. (Ziemann et al. (1996b), with permission).

motor threshold are dependent on ion channel conductivity and reflect membrane excitability. Therefore, information concerning the mechanism of action of drugs (ion channel blockers vs. neurotransmitter modulators) may be elucidated by TMS and TMS may be useful in assessing drug efficacy in individual patients.

In Tourette syndrome, motor threshold and intracortical facilitation are normal, while the silent period is

shortened and intracortical inhibition is reduced (Ziemann et al., 1997). These abnormalities are mainly seen in patients presenting with tics involving the TMS target muscle of the hand but not in those whose tics are limited to more proximal muscles. It therefore seems that tics are associated with deficient motor inhibition which is compatible with either a basal ganglia disorder affecting motor cortex though disinhibited

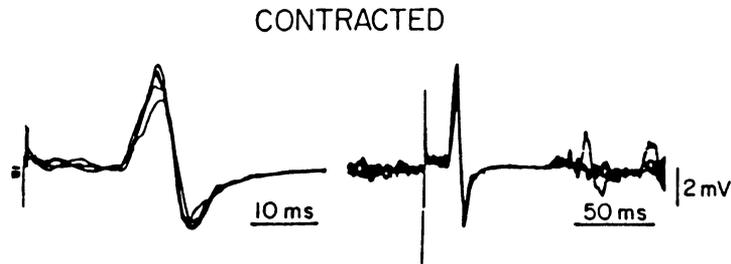


Fig. 4. CMAPs from a digit flexor and the subsequent silent period elicited by TMS of motor cortex during voluntary contraction. The recordings on the right show the duration of the silent period with the return of muscle activity. (Amassian et al. (1990), with permission).

afferents, and/or with impaired inhibition originating in motor cortex (Ziemann et al., 1997).

In a study in which cortical excitability in normal children and children with idiopathic and congenital scoliosis were compared (Domenech et al., 1997), children with idiopathic scoliosis had reduced cortico–cortical inhibition at short (1–4 ms) ISI's compared with children with congenital scoliosis who had findings similar to those seen in normal subjects. In patients with idiopathic scoliosis, cortico–cortical inhibition was 'practically normal on the side of the scoliotic convexity, while it was significantly reduced on the side of the scoliotic concavity.' These findings support the notion that a dystonic dysfunction underlies idiopathic scoliosis. In patients with generalized and even focal dystonia, abnormal cortico–cortical inhibition is found in both cerebral hemispheres.

8. Plasticity

By successively stimulating different scalp locations at close intervals with a figure-eight MC and recording CMAPs from surface electrodes over specific muscles, it is possible to compare amplitude of the CMAPs as a function of the stimulated scalp position and construct a map (Cohen et al., 1991d; Levy et al., 1990b, 1991; Wassermann et al., 1992) (Fig. 5). TMS has been used most often to map the cortical representation of upper extremity muscles (Brasil-Neto et al., 1992; Wassermann et al., 1992). These maps show discrete amplitude peaks within more diffuse overlapping regions. Latencies of the CMAPs tend to be shorter in the center of the map. These peaks may reflect low-threshold areas where the motor neurons projecting to the muscle are most concentrated.

TMS mapping techniques have been used to study the reorganization or plasticity of human motor cortex that follows various types of injury to the peripheral and central nervous system (Levy et al., 1990b, 1991; Cohen et al., 1991a,b,c). These include limb amputations, spinal cord injury, congenital mirror movements, and hemispherectomy. In patients with unilateral upper limb amputation, and also in patients with quadriplegia

and paraplegia secondary to spinal cord trauma, the threshold for TMS is lower, and the area from which CMAPs can be obtained in the spared proximal muscles is substantially enlarged (Levy et al., 1990b, 1991; Cohen et al., 1991a,b,c; Fuhr et al., 1992) (Fig. 5). The map for the spared proximal arm muscles in patients with cervical cord injury expands to include the area that produces CMAPs in distal arm muscles in normal subjects. Enlarged maps for those hand muscles involved in reading Braille have also been demonstrated in blind subjects; this provides evidence for cortical plasticity in neurologically intact individuals as a result of increased use or training (Pascual-Leone and Torres,

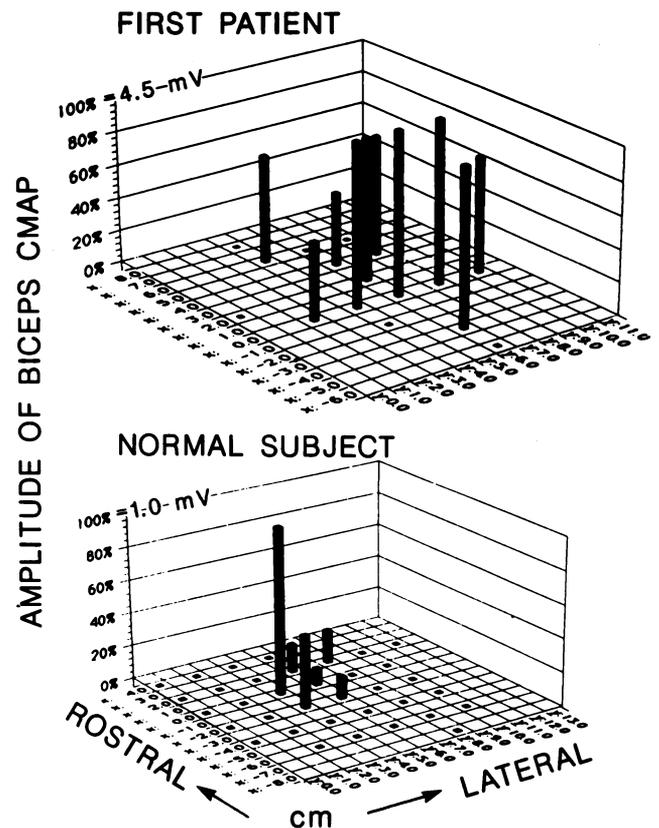


Fig. 5. Comparison of maps for the biceps in a quadriplegic patient (top) and a normal subject (bottom). (Levy et al. (1990b), with permission).

1993). The enlarged motor representation of spared proximal muscles has been reported to occur within 6 days of spinal cord injury (Streletz et al., 1995). Even more rapid changes have been observed in normal subjects within 50 min of acute nerve block produced by occlusion of the circulation in the arm or leg; both the amplitude of the CMAP and the area of proximal muscle representation increased (Brasil-Neto et al., 1993b).

In contrast to TMS, plasticity cannot be demonstrated using electrical transcranial stimulation. Electrical stimulation excites corticospinal tract neurons directly, most likely in the white matter, whereas vertex centered, tangentially oriented TMS excites these neurons transsynaptically. Therefore, excitation of cortical neurons that project to corticospinal tract cells underlies these changes (Brasil-Neto et al., 1993a). In humans, motor thresholds do not significantly change following transient deafferentation of the forearm by ischemic block. However, with paired pulse stimulation, intracortical inhibition at short interstimulus intervals reverses to intracortical facilitation which suggests that disinhibition of preexisting latent synaptic connections is responsible for the plasticity which follows acute deafferentation (Corwell et al., 1997). Previous experimental studies in animals also demonstrated that cortical motor maps are reshaped by unmasking latent intracortical connections (Jacobs and Donoghue, 1991). Sprouting and formation of new synaptic connections may also play an important role in more chronic patients.

9. Tracking flow of symbolic visual information

In an alert individual, the latency to initial vocalization of a visually presented symbol is about 350 ms. Using TMS, this time can be divided into the following intervals: Retina to calcarine cortex and relay from calcarine cortex; arrival of visual representation in frontal lobe; time required for conscious perception and for coding of appropriate motor output for language; frontal lobe activation of laryngeal EMG; laryngeal EMG initiation of voice (Cracco et al., 1996).

A single TMS applied over the occipital area results in transient suppression of visual perception (Amassian et al., 1989b). In these experiments, three random letters were illuminated briefly on a monitor, and TMS was randomly delivered to the occipital cortex 0–200 ms, following the visual stimulus at 20-ms intervals. Perception of the letters was decreased or abolished at TMS pulse delays of 80–100 ms; however, letters were identified correctly at test intervals of less than 60 ms (before the arrival of the visual representation of the letters at the visual cortex) or more than 120 ms (after relay of the visual representation from visual cortex to

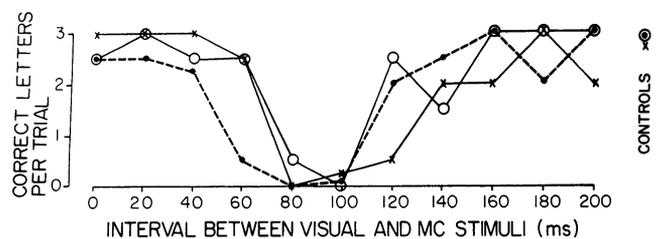


Fig. 6. Effect of TMS of occipital cortex on perception of three letters horizontally displayed. Data from three subjects are shown. (Amassian et al. (1989b), with permission).

other cortical areas) (Fig. 6). It is likely that these cortical inhibitory effects can be explained on the following basis: Intracellular recordings in cat cerebral cortex reveal that electrical cortical stimulation elicits a brief EPSP followed by a prolonged IPSP lasting 80–100 ms in the anesthetized animal. A briefer IPSP lasting about 50 ms would be expected in the alert human subject, and this would explain the inhibitory effects following stimulation of visual cortex (Amassian et al., 1990, 1991a). A similar cause for other inhibitory phenomena seen with TMS seems likely.

TMS of frontal lobe elicit laryngeal CMAPs providing the TMS pulse is triggered by vocal activity which greatly increases the amplitude (i.e. facilitates) of the laryngeal EMG. With voice triggering, laryngeal CMAPs with latencies of 6–8 ms can be recorded from laryngeal muscles following motor cortex TMS. CMAPs with latencies of 10–20 ms are elicited with TMS of the lateral extremity of the precentral gyrus, the region of Broca's area and very medially from presumed supplementary motor area (Fig. 7). Thus transit time from frontal cortex to laryngeal EMG is 6–20 ms depending upon the area of frontal lobe stimulated. Furthermore, the laryngeal CMAP evoked by frontal lobe TMS is increased in amplitude (facilitated) at latencies greater than 130 ms after visual presentation of a numeral suggesting that the representation of the symbol begins to arrive in frontal lobe about 130 ms after its presentation (Amassian et al., 1993; Cracco et al., 1996). The laryngeal EMG typically precedes the beginning of vocalization by 80 ms.

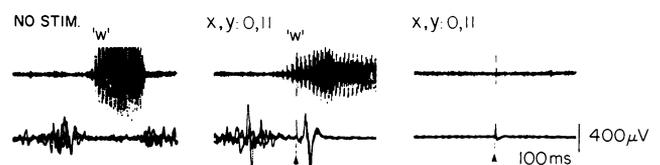


Fig. 7. Facilitatory effect of vocalizing on the external laryngeal CMAP elicited by TMS of left frontal cortex. Paired sweeps, voice (top) and laryngeal EMG (bottom). Left and middle, articulating W; sweep speed such that only initial sound (da) is visible. Middle and right. TMS with and without articulation, respectively. Sweeps superimposed in all records (from Cracco et al. (1996), with permission).

In summary, the 350 ms delay for vocalizing the visual presentation of a numeral includes the retinal–calcarine cortex transfer time (60 ms), relay of the symbolic representation out of calcarine cortex (120 ms), its arrival in and facilitation of frontal cortex (120–140 ms), frontal lobe activation of laryngeal EMG (6–20 ms) and initiation of voice (80 ms). There remains about 125 ms [$350 - (130 + 15 + 80)$] for the visual representation in frontal cortex to be perceived and coded into appropriate motor output for language (Cracco et al., 1996). These data demonstrate that TMS is useful in tracking the flow of information from one brain region to another similar to functional MRI and PET but with superior temporal but inferior spatial resolution.

10. Repetitive TMS (rTMS)

Recently, rTMS, which can stimulate at rates up to 30 Hz, similar to those employed in direct cortical stimulation, has been used to evaluate hemisphere dominance (Pascual-Leone et al., 1991; Jennum et al., 1994). These studies compared rTMS with the intracarotid amobarbital test. rTMS of the dominant hemisphere induced speech arrest and additionally, in some patients, counting errors. Speech localization, using rTMS, showed a high correlation with the results of the amobarbital test. However, it is uncertain whether this will prove to be a reliable method for identifying cerebral dominance because facial and laryngeal muscle contractions are also produced that result in dysarthria and hesitance of speech and make interpretation of results difficult.

A component of central fatigue has been demonstrated using rTMS (Brasil-Neto et al., 1993a). rTMS may also be therapeutically useful; bradykinesia in Parkinson's disease has been diminished (Pascual-Leone et al., 1994) and mood in patients who are depressed has been improved following left frontal lobe rTMS. Very preliminary data suggests that left frontal lobe rTMS may be effective in the treatment of depression (George et al., 1995). A carefully carried out double-blind study is currently being undertaken to support or refute this suggestion.

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