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# Transcranial Magnetic Stimulation: Twenty Years of Stimulating the Human Motor Cortex in Health and Disease

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In the motor system, transcranial magnetic stimulation (TMS) has proved an invaluable tool to study the organisation and interaction of the cortical motor areas. In this review I describe some of the ways in which TMS has been used to map out the major topographical features of the motor output and to test how these change in response motor learning or after peripheral (e.g. amputation) or central (e.g. stroke) injury. More recent work has shown that longer periods of repeated TMS involving several hundred to a thousand pulses can lead to lasting changes in motor cortex excitability that are thought to involve changes in the efficacy of intracortical synapses equivalent to LTP and LTP in slice preparations. These are accompanied by changes in the rate of motor learning and are presently being trialled as potential treatments to speed recovery from stroke.

K e y w o r d s: transcranial magnetic stimulation, TMS, repetitive TMS, virtual lesion, plasticity, stroke rehabilitation, cortical mapping

## 1. Introduction

Although the electrical excitability of nerve and muscle had been known throughout the 18th century, it was not until the experiments of Fritsch and Hitzig (1870) in Germany and David Ferrier (1873) in England that the electrical excitability of the brain was first explored in detail. This work, on dogs and monkeys was followed surprisingly quickly in the following decade by similar observations on the human brain by pioneers such as Bartholow in the USA, Sciamanna in Italy and Alberti in Argentina (see review by [1]). Stimulation was applied directly to the brain through large holes in the scalp of conscious patients that had been caused either by disease (ulceration) or injury. In all cases, faradic stimulation (a form of repetitive stimulation

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with short pulses of current applied repeatedly over a period of a second or two) of the central areas of cortex evoked movements on the opposite side of the body.

Since the beginning of the 20th century, repetitive (usually at 50–60Hz) electrical stimulation of the exposed brain has been used during neurosurgery to document the location of sensory and motor areas of cortex. However, early attempts to stimulate through the intact scalp in conscious individuals proved unsuccessful, mainly because of the local cutaneous pain and scalp muscle contraction produced by strong repetitive stimulation [2]. Only one report exists of successful transcranial repetitive current stimulation in humans [3], although even this is only a brief mention in a paper dedicated to transcranial stimulation in anaesthetised primates.

It was not until 1980 that Merton and Morton [4] successfully showed that transcranial electrical stimulation of the human brain was possible and suitable for routine experimental and clinical application. The secret of their success was that rather than using a long train of repetitive stimulation, they applied just a single, short duration high voltage pulse. In a conscious subjects single stimuli over the motor cortex led to clear movements of the opposite side of the body with a rough somatotopic arrangement corresponding to the "motor homunculus" expected from direct stimulation of the cortex. Stimuli over the occiput elicited visual phosphenes.

The method was used by several groups in the following decade to explore motor cortex function in health and disease, but was limited even when using just single pulses by discomfort produced by contraction of local scalp muscle. However, in 1986, this problem was overcome by the introduction of transcranial magnetic stimulation (TMS) by Barker and colleagues [5]. The stimulator consists of a large electrical capacitance that is attached to a coil of several turns of copper wire. When the circuit is made, the capacitor discharges through the wire causing a large current (around 2000 A is typical) to flow for a 1 ms or so. This current produces a large equally transient magnetic field that is of the same size as that in an MRI scanner. The magnetic field penetrates the scalp and skull easily, and because it changes so rapidly (from zero to a very large value, then back again to zero in 1 ms), it induces electrical ("eddy") currents in the brain under the coil. Effectively the time varying magnetic field "carries" the electrical stimulus in the coil across the barrier of the skull and scalp into the brain. The induced current pulse lasts about 200 μs and is similar in amplitude to that produced by a conventional stimulator applied directly to the surface of the brain.

The magnetic field falls off rapidly with distance from the coil so that it is usually assumed, unless the stimulus intensity is very high that neural activation is limited to elements in the cortex or subcortical white matter. The most likely target of the stimulus is axons of neurones rather than their cell bodies or initial segment regions. Measurements of the strength-duration time constant to produce output from the motor cortex are consistent with this idea [6]. However, since many or most of these axons will have synaptic connections in the cortex, a single stimulus is capable of setting up cascades of activity in cortical circuits that outlast the stimulus pulse by many milliseconds.

A variety of axons belonging to different populations of neurones are activated under the coil [7]. Some are local to the area of cortex under the coil, others project axons to or from the site of stimulation; some will be excitatory, others inhibitory. The final outcome might be complex and quite unlike the normal organised patterns of activity that occur in natural behaviours. However, some selectivity arises from the fact that different neurones have different thresholds to electrical stimulation. Low intensities of stimulation will therefore activate a much more limited population of neurones than higher intensities.

There are two main features of the cortical response to a single TMS pulse and these are readily distinguished in the electromyographic (EMG) recordings of the muscle twitch evoked in a voluntarily contracted hand muscle and the corresponding recordings of the descending corticospinal activity from the spinal cord that are illustrated in Fig. 1. First, a single stimulus evokes a burst of activity that can last for 5–10 ms after the pulse. This is probably due to activity in excitatory intracortical circuits that are activated by the pulse. This burst of activity gives rise to a series of discharges in the corticospinal tract that are known as I-waves (Fig. 1A). The second feature is that the burst is followed by a longer (100–200 ms) period in which activity is suppressed (Fig. 1B). This is probably due to long lasting GABAergic inhibitory input that follows the initial discharge and which suppresses ongoing voluntary activity in the EMG.

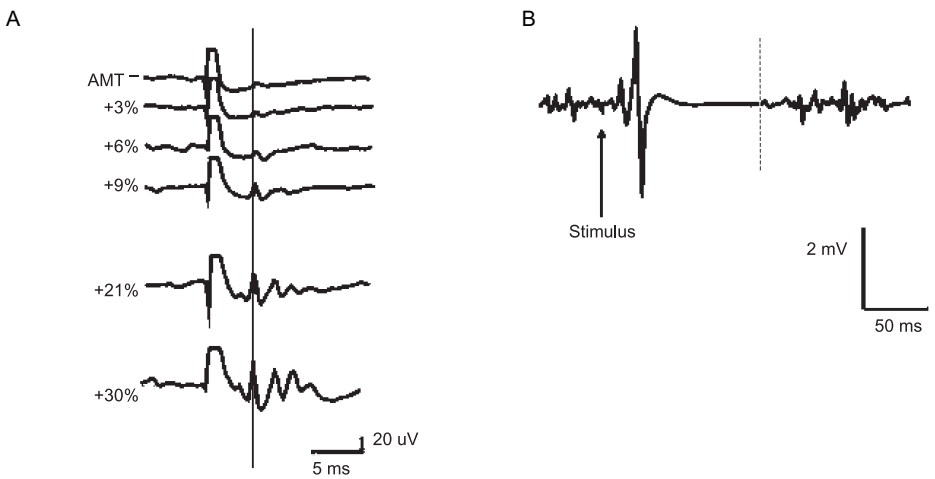


**Fig. 1.** A. Descending volleys evoked by single pulse TMS recorded from the epidural space of the cervical spinal cord in a conscious human subject. Stimulus intensities ranged from active motor threshold (AMT) to AMT + 30% (of max stimulator output). With increasing stimulus intensities a series of waves (I-waves) is recruited. The first of these, termed I1, is indicated by the dashed vertical line. Data kindly supplied by Dr V Di Lazzaro. B. An EMG response recorded while the subject was contracting a small hand muscle (first dorsal interosseous) to a single pulse of TMS at an intensity of 110% resting motor threshold. Approximately 20 ms following the stimulus is a large MEP, followed by a period of relative quiescence of background electromyographic (EMG) activity which is known as the "cortical silent period". The end of the silent period is indicated by the dashed vertical line

## 2. Uses of TMS

Initially TMS was used to explore the corticospinal connection between motor cortex and muscle, with its main clinical application being to document slowing or failure of conduction in central motor pathways in neurological disease, particularly multiple sclerosis. However over the past 20+ years the number and variety of applications has expanded considerably. Four main categories of use can be distinguished: (1) exploration of neural connections in the brain, (2) somatotopic and retinotopic mapping of sensorimotor and visual cortices, (3) the "virtual lesion" method to probe when and where certain types of processing are performed in the brain, and (4) repetitive TMS. I will briefly mention the first three categories before devoting the main part of this chapter to the last one.

### 2.1. Exploration of Neural Connections in the Brain

Stimulation of any area of cortex can lead to activity in axons that project to targets at distant sites. For example, TMS of cortex produces activity in contralateral muscle, a pathway that involves at least 2 synaptic connections (at spinal cord and muscle). The visible muscle twitch or the EMG of the contraction are clear signs of the existence of this connection. However, in other cases more complex methods are needed to monitor activation at sites distant from the point of stimulation [8]. For example, TMS can be combined with EEG or fMRI: TMS of one point on the scalp produces evoked EEG activity at other scalp sites; similarly TMS pulses given in an fMRI scanner lead to changes in BOLD activity distant from the site of stimulation. Technical considerations mean that TMS-EEG is perhaps simpler to combine that TMS-fMRI, although fMRI has the advantage of being able to monitor activity in projections to deep structures such as thalamus, basal ganglia and cerebellum, which are not identifiable in EEG.

In the special case of monitoring inputs to motor cortex from other areas, a simpler method involving a "twin coil" approach is possible [9]. In this case, a standard single TMS pulse is applied to motor cortex to evoke a test MEP in a muscle of interest. Prior to this, a conditioning TMS pulse can be given by a second stimulator at another scalp site. If the conditioning stimulus changes the amplitude of the test MEP, then (with the usual control experiments) we can conclude that there is an influence of the conditioning site on the motor cortex. If the interval at which this happens is short, then the effect is likely to be produced by a direct pathway linking the two.

Paired pulse and TMS-EEG/TMS-fMRI have been used to show changes in the excitability of functional connections in the brain in disease, and can document time varying effects that happen during the performance of a task. Effectively they provide a temporal map of functional connectivity.

### 2.2. Cortical Mapping with TMS

As noted above, TMS of the motor cortex shows a rough scalp somatotopy that is consistent with the classical notions of the motor homunculus, with leg muscle contractions elicited from near the vertex, hand muscles more lateral and facial muscles further lateral still. Although the size of the TMS coils limits the resolution of such maps, careful averaging of the effects from stimulation of a number of scalp sites, together with co-registration of the maps onto the MRI of individual subjects can lead to surprisingly accurate representations of motor cortex. Visual cortex can also be mapped in the same way by asking subjects to indicate the location of phosphenes evoked by stimulation at different occipital sites.

Such mapping experiments can reveal changes in organisation of cortex in disease or after stroke, and can document reorganisation over time.

### 2.3. TMS and "Virtual Lesions"

TMS to any part of the cortex produces a non-physiological pattern of activity that interferes with any ongoing functions that may be occurring at the time of stimulation [10]. The concept has been used widely in cognitive neuroscience to probe when and where different parts of the brain contribute to processing particular tasks. The simplest and first-documented example is stimulation over the visual cortex (at intensities less than required to produce a phosphene). If subjects are presented very briefly (for a few milliseconds only) with a dim visual stimulus, perception is disrupted when TMS is applied 80–120 ms or so after stimulus onset. The TMS pulse has disrupted activity in visual cortex at the time the visual information arrives and this creates a short-lasting "scotoma" in the visual field [11].

This approach is often used to ask whether a site of activation identified in a functional imaging experiment is necessary for task performance or whether it is associated, but not necessary for the task. For example, imaging studies of early blind individuals show activity in visual cortex when they read Braille letters, whereas there is no activity in blindfold sighted subjects. To test whether the activity in blind subjects was contributing to their (superior) performance, TMS was applied over the visual cortex. It disrupted performance in the blind subjects but not in the sighted subjects [12].

## 3. Repetitive TMS (rTMS)

It has been known for many years from animal studies that repeated stimulation of a neural pathway can produce lasting changes in excitability of synaptic connections within that pathway. Typical of these effects are synaptic long term potentiation (LTP)

or long term depression (LTD). Although these effects have been most extensively described in experiments on hippocampus, they have been observed in many other regions, including cerebral cortex.

The first TMS devices could only apply single stimuli once every 4s or so, but within a few years repetitive stimulators became available that could give stimuli at rates of up to 50 Hz or more. As in animal experiments, there is accumulating evidence that repeated cortical stimulation may lead to long term changes in synaptic connections resembling LTP/LTD. However, because rTMS can potentially cause epileptic seizures, strict safety guidelines have been formulated for use in healthy volunteers so that the range of rTMS protocols that have been studied so far is relatively small [13].

The evidence that rTMS can change the excitability of synaptic connections in human brain comes from the study of the after-effects that follow a session of stimulation. These after-effects can be measured in various ways including effects on fMRI activation patterns or behavioural performance. For example, 1500 pulses of motor cortex TMS at given at a frequency of 1 Hz and an intensity subthreshold for evoking any visible movement of the body reduce the excitability of the motor cortex for 20–30 min after the end of the rTMS. Electrophysiologically this is detected as a reduction in the size of the muscle twitch that is evoked by a single standard suprathreshold TMS pulse. Behaviourally it leads to a small increase in the reaction time of movements made by the opposite hand [14] (see also Fig. 2).

The nature of the after-effects of rTMS depends on the number, intensity and pattern of stimulation pulses [9]. For example, stimulation at frequencies higher than 1 Hz tends to increase rather than decrease motor cortex excitability. After-effects also depend on the pattern of the pulses applied. A new protocol termed "theta burst stimulation" (TBS) applies three pulses at 50 Hz at an interburst frequency of 5 Hz (i.e. the theta rhythm of EEG terminology) [15]. At low intensities this produces suppression of motor cortex excitability; however, rather than giving one long period (usually 40s) of TBS, if each TBS is applied only for 2 s followed by a pause of 8 s and then repeated, the effect becomes facilitatory.

It is difficult in humans to obtain direct evidence of the mechanisms responsible for the after-effects of rTMS. Short term effects in the order of seconds or a few minutes could be due to changes in neural excitability caused by shifts in ionic balance around populations of active neurones, or even to electrical capacitative effects storing charge induced by the stimulus. There might also be changes in reafferent feedback to the site of stimulation from its target structures. Thus, suprathreshold rTMS of motor cortex produces muscle twitches that feedback sensory information to the motor cortex and modify its response to stimulation. Again, these effects should disappear quickly after rTMS stops.

One possible candidate for longer lasting changes are LTP and LTD-like effects at cortical synapses. The evidence for this comes from pharmacological interventions in humans showing that the after effects of rTMS depend on the glutamatergic NMDA

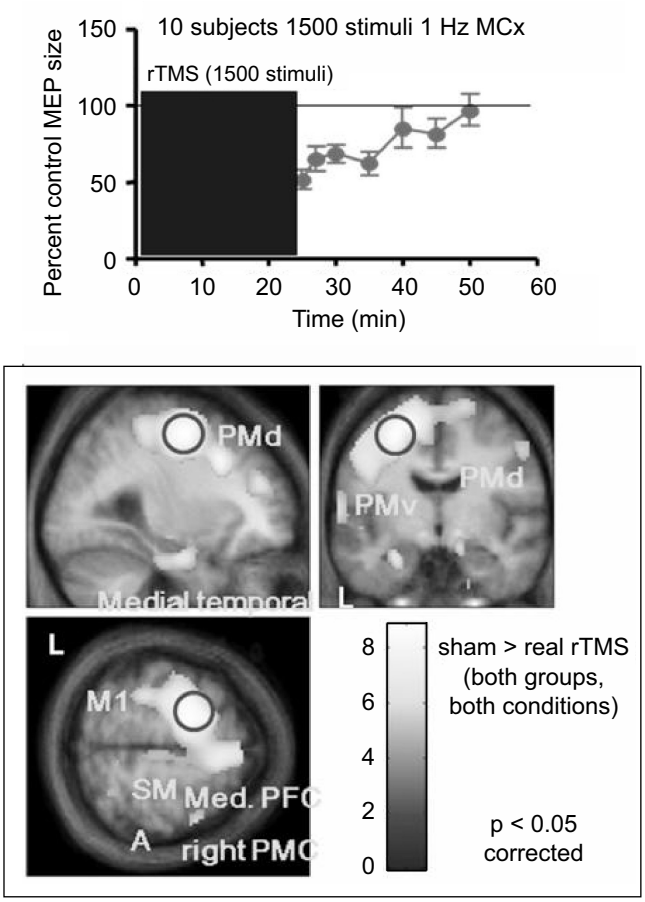


**Fig. 2.** Top: Time course of changes in excitability of the motor cortex after 25 min rTMS at 1 Hz and an intensity of 90% resting threshold. Data plots the amplitude of the EMG response to a single TMS pulse as a percent of the amplitude prior to rTMS. The response is suppressed immediately after rTMS and this effect persists for the next 30 min. Data from [14]. Bottom: Sections of brain from an experiment using positron emission tomography (PET) to measure metabolic activity in a group of healthy subjects and patients with dystonia. Here the results from both groups are combined and the colour coding shows where activity after a 25 min session of real 1 Hz rTMS over dorsal premotor cortex (PMd) is less than that seen after a sham rTMS session. There are significant decreases in activity after real rTMS at the site of stimulation (outlined by circle) as well as at many distant sites. From [22]

receptor, as they are blocked by a single dose of the NMDA receptor antagonist dextromethorphan. Another NMDA receptor antagonist, memantine, can block the suppressive and facilitatory effects of other rTMS protocols [16].

There are now many protocols of rTMS that produce after-effects on the brain. In all cases it is important to remember a number of highly important findings:

1) rTMS not only has effects at the site of stimulation, it also leads to changes

in areas distant from that site, probably by changing activity in afferent and efferent projections. The result is that the after effects cannot equivocally be attributed to changes in the area to which rTMS is applied.

2) The effects of rTMS are variable. They are influenced by the prior history of brain activation, hormones and drugs, and even the genetic characteristics of the individual being tested [17].

### 3.1. Therapeutic Uses of rTMS

Given the possibility that rTMS can alter the efficiency of synaptic connections in the human brain, there have been a large number of investigations into its possible clinical application. The first and largest number of studies have been performed in patients with depression [17]. The rationale comes from the fact that several sessions of ECT are highly effective in treating depression. It is thought that repeated stimulation of the brain somehow leads to long term changes in organisation that ameliorate clinical symptoms. However, the method is limited by unwanted side effects on memory. The question is can several sessions of sub-convulsive rTMS also cause long term effects that might also reduce symptoms of depression without evoking unwanted side effects?

Despite a large number of trials on many thousands of patients, the answer is still somewhat equivocal, with the most recent analyses suggesting that there may be a small to medium effect, particularly in certain subpopulations of patients. In a previous review [17] we pointed out that in retrospect depression was not the ideal condition in which to test the effectiveness of rTMS. Depression is phenotypically diverse with difficult diagnostic criteria and a subjective clinical evaluation that makes it highly susceptible to any placebo effects of rTMS. More recently attention has been drawn to other conditions in which measurement of the effect as well as the rationale for using rTMS are much clearer.

### 3.2. rTMS as a Therapy in Rehabilitation after Motor Stroke

A number of studies have been performed to test whether a single or multiple sessions of rTMS to the motor cortex can improve recovery in the acute and chronic phases after stroke [18]. Two approaches have been used: in the first an excitatory rTMS protocol is applied to the affected hemisphere in order to increase its contribution to recovered movements; in the second, inhibitory rTMS is applied to the non-stroke hemisphere in an attempt to prevent it inhibiting activation of the stroke hemisphere and again improve involvement of the stroke hemisphere in movement.

Single session studies in which motor performance of patients has been examined before and after rTMS have generally shown a 10% or so improvement compared to a placebo rTMS in chronic patients; there have been no single session studies in acute cases given the day to day variation in their symptoms. Daily treatments for

one or two weeks have also been applied in order to give an effect that might last days or months. Both chronic and acute studies have been successful with 10–20% improvement in hand and arm function lasting several weeks after the stroke.

An example of these approaches is shown in Fig. 3 from Khedr et al. [19]. In this study, 52 patients up to 2 weeks after stroke were assigned randomly to real and sham rTMS. Otherwise they continued their normal treatment throughout. Each patient received rTMS (ten 10 s trains at 3 Hz separated by 50 s) at noon every day for 10 days, and was assessed before (blind rater), on 10th day of treatment and 10 days later with the Scandinavian stroke scale (SSS), NIH stroke scale (NIH) and Barthel index (BI). As can be seen, in these acute patients, even the sham rTMS group improved ratings on all scales. However, the real rTMS group improved more and this improvement was sustained up to 10 days later.

Individual subject analysis suggested that patients with the largest strokes failed to benefit from rTMS. In addition the improvement after rTMS was not related to improvement in measures of corticospinal excitability. The conclusion was that rTMS might have been acting at the cortical level by increasing the contribution of undamaged tissue to movement control. Unfortunately the patients were not followed up subsequently so that the final outcome of the two groups is not known. Neverthe-

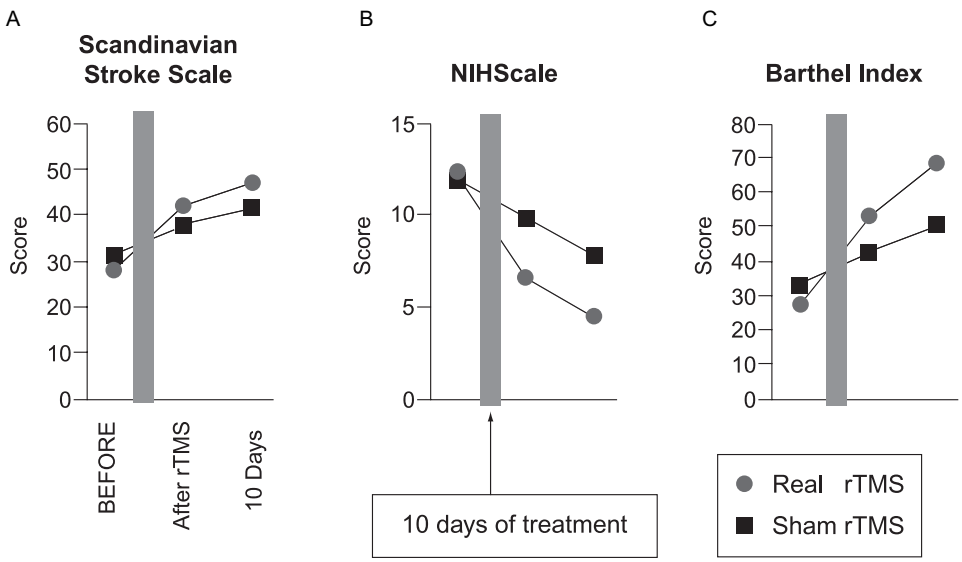


**Fig. 3.** Changes in mean (±SD) clinical scores at the three assessment points for the two groups of patients. The first assessment was immediately prior to commencing rTMS treatment, the second assessment was immediately after the last (tenth) session of rTMS, and the third assessment was 10 days later. A shows data from the Scandinavian Stroke Scale, B shows data from the NIH Stroke Scale, and C shows data from the Barthel scores. Filled circles (●) show data from real rTMS group; filled squares (■) show data from sham treatment group. Improvement was greatest in the real rTMS group for all three scores. Data from [19]

less, the fact that rTMS appeared to speed improvement, even if the final amount turned out to be the same, would be useful in allowing patients to return home from hospital earlier than they might have done.

### 3.3. Possible Mechanisms of rTMS in Stroke Rehabilitation

Studies in animal models of small cortical strokes have shown that hand function recovers more rapidly if primates are given subthreshold continuous repetitive electrical stimulation of the motor cortex during their daily therapy sessions. It appears that the stimulation promotes a more rapid reorganisation of undamaged cortex and that this may contribute to improved function [20]. Perhaps the same may occur in human patients after treatment with rTMS.

It is not known, though, how rTMS might promote more rapid recovery at a cellular level. It may be linked to the mechanisms that promote recovery during active therapy sessions. Such sessions effectively train patients to acquire additional motor skills that they have lost due to stroke. We know that motor learning can occur within the motor cortex and that it involves, at least in healthy animals, LTP and LTD at intracortical synaptic connections [21]. Active relearning after stroke is likely also to involve such "rewiring" of internal connections in order to maximise the use of remaining corticospinal output connections.

How could rTMS given prior to normal therapy improve the behavioural relearning/rewiring in stroke? It is unlikely that rTMS on its own can change the effectiveness of exactly the synapses that are necessary for behavioural gains. rTMS is far too non-specific for that. A more likely possibility is that rTMS increases the excitability of neurones in the cortex and this makes them more likely to discharge during therapy sessions. Changes in synaptic efficiency require that neurones discharge when they receive patterned inputs: repeating this process many times then leads to changes in the effectiveness of the synapses that are responsible for the discharge. If the cells are so unexcitable that they do not discharge on receiving input, then there can be no changes in synaptic strength, and no learning. Thus, rTMS by increasing the probability of discharge may simply increase the probability of synaptic learning.

## 4. Conclusions

There is now reasonable evidence that rTMS can produce changes in the effectiveness of synaptic connections in the brain. At the moment the effects in normal subjects are relatively small, short lasting (e.g. 30–60 min), and variable. There is also evidence that repeated sessions of rTMS in patient groups might have therapeutically useful effects on function in a variety of disease states. What is needed now is more information of how these behavioural gains are produced so that we can design methods to maximise the clinical utility of rTMS and remove its variability.

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