REVIEW

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# Transcranial magnetic stimulation: new insights into representational cortical plasticity

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Abstract In the last decade, transcranial magnetic stimulation (TMS) has been used increasingly as a tool to explore the mechanisms and consequences of cortical plasticity in the intact human cortex. Because the spatial accuracy of the technique is limited, we refer to this as plasticity at a regional level. Currently, TMS is used to explore regional reorganization in three different ways. First, it can map changes in the pattern of connectivity within and between different cortical areas or their spinal projections. Important examples of this approach can be found in the work on motor cortex representations following a variety of interventions such as immobilization, skill acquisition, or stroke. Second, TMS can be used to investigate the behavioural relevance of these changes. By applying TMS in its "virtual lesion" mode, it is possible to interfere with cortical function and ask whether plastic reorganization within a distinct cortical area improves function. Third, TMS can be used to promote changes in cortical function. This is achieved by using repetitive TMS (rTMS) to induce short-term functional reorganization in the human cortex. The magnitude and the direction of rTMS-induced plasticity depend on extrinsic factors (i.e. the variables of stimulation such as intensity, frequency, and total number of stimuli) and intrinsic factors (i.e. the functional state of the cortex targeted by rTMS). Since conditioning effects of rTMS are not limited to the stimulated cortex but give rise to functional changes in interconnected cortical areas, rTMS is a suitable tool to investigate plasticity within a distributed functional network. Indeed, the lasting effects of rTMS offer new possibilities to study dynamic aspects of the pathophysiology of a variety of diseases and may have therapeutic potential in some neuropsychiatric disorders.

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# Introduction

The adult mammalian cortex maintains a considerable potential for functional reorganization throughout life (see for review: Buonomano and Merzenich 1998; Sanes and Donoghue 2000). The mechanism of this reorganization can be studied on three levels (Buonomano and Merzenich 1998): (1) at the level of the synapse, investigating changes in parameters such as excitatory postsynaptic potential (EPSP) amplitudes; (2) at a cellular level, exploring changes in the responses of single neurons following short-term conditioning protocols; and (3) at a regional level, where plasticity results in changes in the response of larger cell assemblies following lasting changes of inputs induced by training, lesions, or other manipulations.

While current knowledge about cortical plasticity at a synaptic or cellular level is based entirely on animal data, representational plasticity at a regional level has been successfully explored in vivo in the intact human brain (Buonomano and Merzenich 1998). In the last decade, much of this work has used non-invasive neuroimaging techniques to investigate the spatial pattern and the time course of representational plasticity in the human brain. Here we review the contribution of transcranial magnetic stimulation (TMS) in this field.

TMS is produced by passing a very brief high-current pulse through an insulated coil of wire held over the scalp (see for review: Barker 1999). The electric pulse induces a rapidly changing magnetic field with lines of flux running perpendicular to the coil. Since the skull has little impedance to the passage of the magnetic field, it passes readily into the brain where it induces electric currents that flow at right angles to the magnetic field. If current amplitude, duration, and direction are appropriate, they will depolarize cortical neurons and generate action

Table 1 Summary of the	e different approaches	that can be ad	opted to investigate	representational	plasticity of th	e human	brain w	ith
transcranial magnetic stin	mulation (TMS)							

	Method	Functional system	Type of TMS			
1	Exploring dynamic changes of functional representation					
1.1 1.2 1.3	Mapping corticomotor representations Assessing changes in cortiocomotor excitability Assessing changes in phosphene threshold	Executive motor system Executive motor system Visual system	Single-pulse TMS Single-pulse/paired-pulse TMS Single-pulse/paired-pulse TMS			
2	Assessing the functional relevance of representational reorganization					
2.1 2.2	Disruption of a distinct brain function <sup>a</sup> Improvement of a distinct brain function <sup>a</sup>	Large-scale functional networks Large-scale functional networks	Single-pulse, paired-pulse TMS Short trains of repetitive TMS			
3	Promoting representational plasticity with repetitive transcranial magnetic stimulation					
3.1 3.2 3.3	Conditioning of cortical excitability Lasting modulation of a distinct brain function <sup>a</sup> Imaging rTMS-induced functional reorganization	Motor and visual system Large-scale functional networks Large-scale functional networks	Repetitive TMS Repetitive TMS Repetitive TMS			

<sup>a</sup> TMS is capable of modulating a variety of brain functions, including perception, motor control, mood, and cognition

potentials (Rothwell et al. 1999). Thus, the term "magnetic cortex stimulation" is somewhat misleading, since the magnetic field simply serves as a "vehicle" for carrying an electric stimulus across the scalp and skull into the cortex; it is an electric current which actually excites cortical neurons.

The site of stimulation is not very focal. For example, with a standard 9-cm-diameter circular coil, activation occurs maximally in an annulus of the same size under the coil. Figure of eight coils are wound so that the current induced under the midregion is twice that under each of the edges (Barker 1999). Even so, in many coils this midregion is up to 4 cm long, potentially activating a similar area within the brain.

In contrast to other techniques that provide a record of brain activity, TMS can interact with and even change the pattern of neuronal activity in the cortex. However, it is important to bear in mind that TMS will activate a range of neural elements in the stimulated area of cortex, and this can lead to a mixture of both excitatory and inhibitory effects. In addition, some of these elements may project to cortical and subcortical targets, producing actions at a distance from the site of stimulation. Since stimulation is neither very focal nor well defined with regard to the subsets of cortical neurons being activated by TMS, TMS studies on cortical reorganization, just like functional imaging studies, provide information about reorganization at a (inter-) regional level rather than synaptic plasticity at a neuronal level. This is not to say that rTMS is not capable of inducing synaptic plasticity at a cellular level. As described later in this review, some animal experiments have provided evidence that rTMS induces synaptic plasticity. Similarly, rTMS induced changes in excitability of the human primary motor cortex have many properties common to long-term potentiation and depression.

At present, TMS is used in three complementary ways to investigate the plasticity of the human cortex (Table 1). First, single and paired pulse TMS techniques can describe changes in the excitability of cortico-cortical and cortico-subcortical connections. Most of these studies have been performed on the motor cortex following immobilization, skill acquisition, or stroke. Second, TMS can be used to disrupt activity in any cortical area ("virtual lesion") to explore the functional relevance of cortical reorganization. Third, repetitive TMS (rTMS) can produce changes in excitability of cortical circuits that outlast the period of stimulation, opening the possibility of intervening directly with the mechanisms of cortical plasticity in the intact human cortex.

When TMS is used in humans, specific safety issues need to be taken into account, in particular when regular trains of TMS are applied. The main risk of TMS is to induce epileptic seizures, especially if rTMS is applied at high frequency and intensity to the cortex. However, the risks can be minimized by careful selection of the participants and strict adherence to safety guidelines (Hallett et al. 1999). A detailed discussion of the safety aspects of TMS is beyond the scope of this paper. We refer the reader to a comprehensive review by Wassermann et al. (1998).

# Exploring changes in functional organization of the corticospinal motor system

The primary motor cortex has been used extensively for TMS studies. This is because the effects of stimulation are easy to quantify by measuring the size of EMG responses evoked in contralateral muscles (MEPs). Although the MEP may look similar to a compound muscle action potential (CMAP) evoked by supramaximal electric stimulation of peripheral nerve, it is a more complex event (Magistris et al. 1998). Not only is the site of stimulation at least two synapses distant from the muscle, but a single TMS pulse produces repetitive activity in cortex that sets up a series of descending volleys in large diameter corticospinal axons. The combination of repetitive activity in central and peripheral motor axons, temporal dispersion and variable levels of excitability at intervening synapses all combine to make the MEP much more variable than the CMAP (Kiers et al. 1993).

Methods for mapping corticomotor and cortico-cortical connections

#### Mapping studies

TMS with a focal figure of eight coil can be used to demonstrate the gross somatotopy of the motor homunculus. Stimuli are applied at various scalp sites using a latitude/longitude based coordinate system referenced to the vertex (Cohen et al. 1991; Wassermann et al. 1992, see for review: Thickbroom et al. 1999), and the amplitude of MEPs evoked in contralateral muscles is measured. This gives a "map" of sites on the scalp from which responses can be obtained in each muscle of interest. The two most important parameters of such maps are the centre of gravity (i.e. an amplitude-weighted centre of the map) and the "hot spot" (the point of maximum response). The centres of gravity or hot spots of proximal to distal muscles of the upper extremity usually line up in a medial to lateral location along the central sulcus, suggesting that they give a good estimate of the site of the centre or most excitable region of the underlying corticospinal projection.

The area of the map is more difficult to interpret since the site of stimulation with TMS is considerably less focal than that excited via electrodes placed on the cortical surface. The area of a TMS map is therefore a function of both the area of the underlying corticospinal map and the distance from the coil that corticospinal neurons can be activated. One consequence of this is that the higher the intensity of the TMS stimulus, the larger the area of the MEP map. In addition, the higher the excitability of the cortical neurons, the easier it will be to stimulate them at a distance from the coil. Again, the apparent area of the MEP map will be larger than if excitability is low.

Levels of excitability are particularly problematic in mapping studies that are carried out in subjects who are at rest. The excitability of the corticospinal system in subjects at rest is ill defined: neurons can be quiescent because they are 1 mV from firing threshold or because they are 10 mV from threshold. In the former case their excitability will be much higher, and the MEP map much larger than in the latter. It is not only cortical excitability that must be defined: the area of MEP maps also depends on the excitability of spinal mechanisms. Imagine a coil activates a portion of the corticospinal projection to a muscle that produces a 1-mV EPSP in spinal motoneurons. If these neurons are far from their threshold, they will not discharge and no MEP will be recorded. The stimulation point on the scalp will be outside the area of the MEP map. Conversely, if spinal excitability is high, the same EPSP will discharge the motoneuron and produce an MEP. The cortical point will then be classified as inside the cortical map.

An alternative to mapping MEP excitability is to map the threshold for evoking a specific movement at particular scalp locations (Classen et al. 1998). The movement evoked will be related to the first recruited muscle at the point of stimulation. If several muscles acting on the same joint are recruited simultaneously, then the movement evoked will depend on the strength and mechanical advantage of the muscles about the joint. Relatively discrete and reproducible movements can be evoked in distal hand muscles, but this is rarely possible for more proximal muscles because of their higher threshold.

TMS mapping studies can also be carried out using other measures. For instance, the duration of the cortical silent period or the TMS-induced delay in voluntary movement can be used to map inhibitory effects of TMS (Wilson et al. 1993; Taylor et al. 1995; Thickbroom et al. 1996). Finally the advent of stereotaxic devices for accurate positioning the magnetic coil has allowed noninvasive mapping of the spatial representation of cognitive functions, such as sensorimotor mapping or visual search.

#### Threshold and input/output curves

Cortical motor threshold is defined as the minimum intensity that produces an MEP in the target muscle on 50% of trials (Rothwell et al. 1999). It is a complex measure since although the initial cortical elements activated by TMS are likely to be large-diameter myelinated axons, MEPs are evoked only after a sequence of synaptic relays in both cortex and spinal cord. Thus, although the threshold of the cortical axons is likely to be relatively dependent of the level of synaptic activity in the cortex, the MEP threshold will also depend on the excitability of synaptic relays. As we have seen above, excitability is not well defined at rest, so that threshold is probably best measured during active muscle contraction, when synaptic activity is better defined. Under such circumstances, Ziemann et al. (1995, 1996a, 1996b, 1996c) have shown that threshold is affected by administration of CNS acting drugs that affect membrane excitability, whereas drugs that affect synaptic transmission have little influence. This effect on axonal excitability is probably responsible for the increased MEP threshold seen in patients treated with antiepileptic drugs.

Input/output curves measure the amplitude of MEPs at a range of stimulus intensities (Devanne et al. 1997; Ridding and Rothwell 1997; Carroll et al. 2001). For hand muscles, these are usually sigmoidal with a steeply rising slope and final plateau; for other muscles, the slope is more linear and the plateau may not be reached even at maximal stimulator output (Kischka et al. 1993; Devanne et al. 1997). The slope of the curve depends on the distribution of excitability within the corticospinal pathway and the spatial distribution of excitable elements in the cortex under the stimulating coil. As an example, imagine a situation in which all the elements that facilitate projections to muscle X are equally excitable, and distributed evenly over the entire surface of the motor cortex. A coil placed over the middle of the motor area would excite those elements immediately beneath the junction region, and as the stimulus intensity was

increased the stimulus would spread to activate elements further away from the coil. As long as the corticospinal effects on spinal motoneurons were equally effective from all sites, the slope of the input/output curve would be a function of the physical spread of stimulus from the coil. Conversely, imagine that all facilitatory elements were clustered in a very small area under the junction of the coil, but that some elements were easy to excite whereas others required a high stimulus intensity. In this case (again assuming equal spinal effects from all elements), the slope of the input/output curve would give a measure of the distribution of excitability in the cortex.

Changes in the input/output curve over a period of time may be due either to changes in the distribution of excitability in the corticospinal system, or to changes in the spatial distribution of excitable elements in the cortex. In this respect, they provide information very similar to that from mapping studies. However, only mapping can reveal asymmetric changes in spatial distribution. For example, if a procedure (e.g. anaesthesia) increases the excitability of the lateral elements of a cortical population, whilst that of the medial ones stays the same, it will be evident as a shift in the centre of gravity of a cortical map. In contrast, the change in slope of input/output curve will be indistinguishable from a mild increase in excitability of all the elements.

#### Measures of cortical inhibition

MEP measures represent the net facilitatory effect of a TMS pulse. Two methods provide complementary information on the excitability of cortical inhibitory circuits. The silent period is the period of suppressed EMG activity that follows an MEP evoked in actively contracting muscle. It is due to a combination of spinal and cortical effects (Fuhr et al. 1991). In the spinal cord, motoneurons that fire in the MEP are refractory to voluntary activation via descending corticospinal neurons for 50-100 ms, and, in the same period, feedback from the contracting muscle can also produce reflex effects on spinal excitability. However, such changes last only 100 ms or so after the MEP, whereas the silent period can be much longer, especially at high intensities of stimulation (Fuhr et al. 1991). The extra period of inhibition is due to suppression of cortical excitability, probably through the action of a long lasting GABA<sub>B</sub>ergic IPSP (Siebner et al. 1998; Werhahn et al. 1999). Measurements of the duration of the silent period are thought to give an estimate of the excitability of this system.

The silent period is evoked by relatively high stimulus intensities. However, a different inhibitory system can be activated at much lower intensities. Kujirai et al. (1993) demonstrated that the MEP evoked in resting muscle could be suppressed if it was preceded by a subthreshold stimulus given 1–5 ms earlier. Increasing the interval to 10–20 ms resulted in facilitation of the MEP. Ziemann and colleagues (1995, 1996b, 1996c) have used centrally acting drugs to show that the initial period of inhibition is

GABAergic, probably due to activity in a  $GABA_A$  system.

Patterns of functional reorganization in the corticospinal system

In healthy subjects, TMS maps of the motor cortex change following a variety of experimental conditions, including immobilization, motor learning, peripheral sensory stimulation or temporary peripheral deafferentation (Cohen et al. 1991; Brasil-Neto et al. 1992; Pascual-Leone et al. 1993, 1994a, 1995, 1996a; Liepert et al. 1995; Ridding and Rothwell 1995; Ridding et al. 2001; Zanette et al. 1997). However, in all these cases, the maps have been made in resting subjects and the major effect has been an increase in the size of the map, which may well indicate that there has been an increase in excitability of the corticospinal projection rather than a true reorganization. This would be consistent with the finding that the changes in map area are no longer seen if the maps are made during a voluntary contraction of the target muscle (Ridding and Rothwell 1995). Voluntary contraction presumably normalizes levels of excitability so that differences due to subthreshold levels of excitability disappear.

There are, however, a small number of studies that show changes in map area when made during contraction (Byrnes et al. 1998; Wilson et al. 1995). Presumably, in these instances it is more likely that a change in cortical connectivity has occurred.

Whether mapping studies have focused on excitability or on location, one of the main findings has been that both features can be readily influenced by the level of sensory feedback. For example, removing feedback in healthy subjects by temporary anaesthesia can increase excitability of corticospinal projections to muscles proximal to the block (Brasil-Neto et al. 1992; Ridding and Rothwell 1997). The effect occurs during the period of anaesthesia but returns to normal shortly after the block. However, other types of sensory manipulation can cause long lasting changes. Both Hamdy et al. (1998b) and Ridding et al. (2000, 2001) have shown that stimulation of peripheral sensory afferents for several minutes can lead to changes in MEP maps that last 30–60 min after the end of sensory stimulation. Paired stimulation of peripheral afferents and TMS of sensorimotor cortex can also lead to similar long lasting changes in corticospinal excitability (Stefan et al. 2000).

Classen et al. (1998) showed that repeated practice of an isolated thumb movement could alter the excitability of the corticospinal projections to thumb muscles. They positioned a figure of eight coil so that it evoked an isolated thumb movement in a reliable direction. They then asked subjects repeatedly to practice moving the thumb in the opposite direction. After several minutes of practice, TMS was reapplied and the evoked direction of movement shifted to the practiced direction. They did not test how much of this effect was due to activation of



cm +++++++

**Fig. 1** Topographical maps of cortical representation of the pharynx in two patients (non-dysphagic and dysphagic) who were studied with single-pulse TMS at initial presentation and at 3 months after a right hemisphere stroke (modified with kind permission from Hamdy and Rothwell 1998). All plots are oriented as indicated by the letters with the right and left scalp grids viewed from above (A anterior, P posterior, R right, L left). Marked increments on the axes represent distance along coronal (R-L) and sagittal (A-P) axes (in centimetres) of the cortical grid. The non-dysphagic patient (*upper panels*) had normal swallowing throughout, whereas the dysphagic patient had evidence of aspiration on

sensory afferents from the practiced movement and how much was due to the motor practice itself. The effect was termed "use-dependent" plasticity. It was an impressive demonstration of a shift in cortical excitability produced by natural inputs.

Premedication with dextromethorphan (a *N*-methyl-Daspartate receptor blocker) and lorazepam (a positive allosteric modulator of GABA type-A receptors) substantially reduced use-dependent plasticity, indicating that *N*methyl-D-aspartate receptor activation and GABAergic inhibition may be involved (Butefisch et al. 2000; Ziemann et al. 2001). Ziemann et al. (2001) went on to investigate the effect of an ischaemic nerve block on usedependent plasticity. They demonstrated that temporary deafferentation/deefferentation of the limb is capable of enhancing use-dependent plasticity in a limb muscle proximal to ischaemic nerve block. This finding provides evidence that the sensory input to the sensorimotor cortex modifies cortical susceptibility to functional reorganization.

A major question that is relevant to the possible therapeutic application of these techniques is whether these changes in cortical maps are associated with any behavioural effects on control of movement. The studies of Hamdy et al. on swallowing provide one example of the possible benefits of long term changes in cortical MEP maps. They showed in healthy subjects that there was somatotopic arrangement of the various swallowing muscles and an asymmetric representation for swallowing between the two hemispheres (Hamdy et al. 1996). In stroke patients, damage to the hemisphere that has the greater representation of swallowing corticospinal output

videofluoroscopic evaluation at presentation, but recovered normal swallowing by 3 months. Cortical mapping revealed that the dysphasic patient (*lower panels*) had a less excitable area of pharyngeal representation on the unaffected hemisphere than the non-dysphasic patient, but by 3 months it had enlarged to be comparable with that of the non-dysphasic patient. By contrast, on the affected hemisphere of both patients, the area of pharyngeal representation was small and remained unchanged with time. The *vertex of each plot* is marked by a "+". The intensity scale shown *on the right* is colour-coded as a percentage of the amplitude of the maximum response for each muscle group in each patient

appears to predispose that individual to develop swallowing problems (Hamdy et al. 1996). Sequential TMS mapping after stroke showed that recovery of swallowing function was associated with an enlargement of the cortical representation in the undamaged hemisphere (Fig. 1), suggesting that recovery depends on the presence of an intact projection from the undamaged hemisphere that can develop increased control over brainstem centres over a period of weeks (Hamdy et al. 1997, 1998a; Hamdy and Rothwell 1998). The same group explored the conditioning effects of pharyngeal electrical stimulation on the human swallowing motor cortex in healthy volunteers (Hamdy et al. 1998b). Ten minutes of repetitive electrical sensory stimulation of the pharynx at a frequency of 10 Hz gave rise to a functional reorganization of the swallowing motor cortex, inducing a reciprocal change in the amplitudes of the TMS-evoked pharyngeal and oesophageal responses (Hamdy et al. 1998b). Immediately and 30 min after pharyngeal stimulation, pharyngeal response amplitudes increased, whereas oesophageal amplitudes decreased. Both pharyngeal and oesophageal responses returned to baseline levels at 60 min after pharyngeal stimulation. In healthy subjects, these changes in MEP maps were not accompanied by any obvious change in swallowing function. However, when applied to dysphagic patients after stroke (Fraser et al. 2002), there was significant improvement in swallowing function that correlated with the amount of change in the cortical maps.

A second example of the probable functional effect of these changes in corticospinal excitability comes from studies on patients with limb dystonia following the injection of botulinum toxin (BTX) in clinically affected muscles. Although BTX is thought to work principally by weakening overactive muscle, there is some evidence that there may also be central effects on spinal reflexes (Priori et al. 1995). Recent studies have also shown that BTX produces effects at a cortical level. In patients with writer's cramp, cortical mapping of the MEPs and the TMS-evoked silent period provided some evidence for a reorganization of corticospinal motor output to the affected hand several weeks after BTX injections (Byrnes et al. 1998) and normalization of deficient cortico-cortical inhibition at short intervals (Gilio et al. 2000). All these effects returned towards pretreatment levels as the peripheral effects of BTX wore off. The authors speculated that the changes were secondary to changes in sensory feedback from the weakened limb, but it remains to be clarified whether these modulatory effects on the corticospinal motor system actually contribute to the therapeutic efficacy of BTX.

# Probing the functional relevance of representational plasticity

In addition to recruiting positive phenomena such as the muscle twitch evoked by TMS over the motor strip or phosphenes elicited by TMS of the occipital cortex, TMS is also capable of interfering with the normal pattern of neuronal activity during perception, motor execution, or higher-level cognitive processes (Jahanshahi and Rothwell 2000). This disruptive effect of TMS on cortical function is often referred to as a "virtual lesion" (Walsh and Rushworth 1999), and occurs first because the stimulus transiently synchronizes the activity of a large proportion of neurons under the coil and second because it induces a long lasting generalized IPSP that reduces cortical activity for the next 50–200 ms depending on stimulus intensity.

Experiments that make use of this virtual lesion effect assume that if activity in a cortical area is essential for a task, then a single TMS pulse given at the appropriate time will disrupt performance. When all goes well, TMS can map the pattern and time course of cortical activity in simple tasks (e.g. Terao et al. 1998). In contrast to positive phenomena which can be elicited with TMS only over a very limited set of cortical areas such as the primary motor cortex (e.g. muscle twitch) and the occipital cortex (e.g. phosphenes), disruptive effects on a specific task can be observed over virtually all cortical sites that can be targeted by TMS, including prefrontal, premotor, motor, parietal, temporal, or occipital cortices (Jahanshahi and Rothwell 2000).

There are two main drawbacks to this technique. First, it is necessary to exclude non-specific effects of the noise of the coil discharge and the sensation induced by the stimulus on the scalp on factors such as attention and alertness. These can usually be controlled by comparing the effects of stimulation at different scalp sites ("control sites") and by checking that the effect is specific to the task being investigated ("control tasks"). The second problem is the interpretation of negative results. At present, for most areas of cortex except the primary motor and visual areas, we have no measure of how effectively TMS has activated neurons in the region under the coil. Thus, if TMS has no effect on a task, it may be due to a failure to stimulate the cortex rather than a lack of involvement. In theory, higher stimulus intensities may solve the problem, but because these raise a secondary issue of increased spread of stimulation from the coil centre, many authors use two or more pulses of TMS at short interstimulus intervals to try to increase the effectiveness and duration of the virtual lesion effect.

To date there have been surprisingly few studies in which the disruptive effect of TMS has been used to probe the functional relevance of cortical reorganization after brain injury or in diseases. The first example was that of Cohen et al. (1997), who followed up an observation by Sadato et al. (1996) that primary visual areas were active during Braille reading in congenitally blind but not sighted subjects. To test whether this activity was contributing to performance, Cohen et al. (1997) gave a short train of TMS over the occiput during Braille reading. Occipital TMS interfered with Braille reading in blind subjects, but not in normal subjects, providing functional evidence that the occipital cortex is actively involved in Braille reading in early blind individuals.

TMS can also demonstrate "maladaptive" reorganization that can follow brain injury. Oliveri et al. (1999, 2000) studied poststroke patients with unilateral neglect and showed that TMS over frontal or parietal regions of the left unaffected hemisphere could temporarily reduce contralesional tactile extinction and visuospatial neglect after damage to the right hemisphere. This observation is consistent with the concept that tactile extinction after right-hemispheric damage is caused by an abnormal disinhibition of the unaffected hemisphere, resulting in an imbalance between the bilateral neuronal processes subserving spatial attention. According to this concept, a TMS-induced transient lesion of the unaffected "disinhibited" cortex will temporarily restore the balance between the hemispheres and transiently decrease symptoms of neglect.

Interestingly, beneficial effects of a virtual lesion can be demonstrated in some tasks even in healthy subjects. Walsh et al. (1998b) showed that visual discrimination of stationary coloured stimuli could be improved by transient disruption of the motion sensitive visual area V5, whereas discrimination of moving stimuli was improved by stimulation over V4. The interpretation was that processing of information unnecessary for a particular task can reduce performance. When this processing is disrupted by TMS, performance improves. A similar mechanism may explain why analogic reasoning is enhanced by applying three 10-s trains of subthreshold 5-Hz rTMS over the left prefrontal cortex (Boroojerdi et al. 2001).

Finally, the disruptive effects of TMS on cortical processing can be applied to investigate the functional plasticity associated with learning in normal subjects (Walsh et al. 1998a; Corthout et al. 2000; Muellbacher et al. 2002). Walsh et al. (1998a) investigated the disruptive effect of TMS over the right parietal cortex on a visual search task. After extensive perceptual training, the initially disruptive effect of TMS on task performance disappeared, but disruption reappeared when subjects were tested on a new visual search array. The implication was that regions in the right parietal cortex were involved in the early stages of learning this task, but that continued practice involved consolidation in other cortical areas.

# Modulation of cortical plasticity with repetitive TMS

Although repetitive transcranial magnetic stimulation (rTMS) is sometimes used to disrupt cortical activity for a long period (see above), the majority of applications make use of the fact that periods of rTMS can sometimes produce effects on cortical circuits that outlast the duration of the stimulus (e.g. Hallett et al. 1999). Effectively this provides an opportunity to provoke and study mechanisms of acute cortical reorganization in the healthy human brain.

Long lasting effects of rTMS investigated in the corticospinal motor system

The majority of the descriptive studies of the effects of rTMS have used the primary motor cortex. They have shown that rTMS can have long term effects on corticospinal excitability, but that the direction, magnitude, and duration of the conditioning effects are critically dependent on the stimulation variables. It is important to note that, as with the mapping studies reviewed above, corticospinal excitability is usually measured by evoking MEPs in relaxed muscle. Comparison of the effects when testing during active contraction gives some insight into the possible mechanism of the aftereffects (see below).

Three factors influence the effect of rTMS: frequency, intensity and duration of stimulation. Because of this it is important to specify all three parameters when describing the results of any rTMS experiment. In general, when authors talk of "high-frequency stimulation", they are referring to frequencies of about 5 Hz and above; "low frequency stimulation" refers to frequencies of about 1 Hz. Regarding the strength of stimulation, rTMS at an intensity of more than about 10% above the MEP threshold in relaxed muscle is labelled "high intensity stimulation".

High frequencies of rTMS, especially at high intensities of stimulation, lead to facilitatory aftereffects on corticospinal excitability. A ten-pulse rTMS train at 150% resting motor threshold and 20 Hz caused an increase in MEP size lasting for about 3 min after the administration of rTMS (Pascual-Leone et al. 1994b). A 30-pulse rTMS train at 120% resting motor threshold and 15 Hz caused a shorter and smaller increase in MEP size for 90 s (Wu et al. 2000). Stimulation at intensities below relaxed motor threshold usually requires longer trains before any lasting effect is seen. For example, Maeda et al. (2000a, 2000b) reported a facilitation of MEPs for 2 min after the administration of 240 pulses of 20-Hz stimuli at 90% resting threshold. Notably 10 Hz rTMS had no lasting effect on MEP size.

Low frequency rTMS usually results in suppression of corticospinal excitability. A 15-min train of 0.9 Hz applied at 115% of motor resting threshold over the primary motor cortex reduced corticospinal excitability (i.e. increased resting motor threshold, and suppressed the MEP input-output curve) for at least 15 min after the end of stimulation (Chen et al. 1997; Muellbacher et al. 2000, 2002). Low-frequency rTMS at intensities below relaxed motor threshold have a much weaker effect on corticospinal excitability as compared with suprathreshold rTMS (Fitzgerald et al. 2002). A 240-pulse train of 1 Hz rTMS at 90% of resting threshold reduced MEP amplitude for about 2 min (Maeda et al. 2000a). Even lower intensities (90% active motor threshold) or lower frequencies (0.1 Hz) had no lasting effect (Chen et al. 1997; Gerschlager et al. 2001).

The duration of rTMS affects the duration and depth of the aftereffect. Both Maeda et al. (2000a, 2000b) and Touge et al. (2001) used 1 Hz rTMS at 90% and 95% relaxed threshold respectively. Longer periods of rTMS lead to longer and stronger reductions in excitability.

Studies of relatively short trains (<20 stimuli) of rTMS give an insight into the interaction between factors promoting inhibition and factors promoting excitation (Modugno et al. 2001). Short trains of only four stimuli at frequencies up to 20 Hz and intensities up to 150% resting threshold resulted in a transient inhibition of MEPs for up to 1 s after the end of the train (Modugno et al. 2001). However, if the number of stimuli in the train was increased to 20, then facilitation became prominent at high intensities (Modugno et al. 2001). The authors suggested that the threshold for inhibitory effects was lower than that for facilitation, and that inhibition built up faster than facilitation. The result was that short trains tended to result in transient inhibition whereas longer trains were likely to show facilitation, particularly if the intensity and frequency of stimulation was high.

Although the majority of studies on mechanism of rTMS have used primary motor cortex, preliminary work on occipital visual cortex suggests that the effects may be similar. Boroojerdi et al. (2000) measured the threshold intensity for evoking a phosphene after stimulation over occipital cortex. They found that 15 min of 1 Hz stimulation over the occiput at an intensity of phosphene threshold decreased the excitability of the visual cortex (i.e. increased phosphene threshold) for about 10 min after the end of stimulation.

# Mechanisms of the aftereffect of rTMS on corticospinal excitability

There are two important questions concerning mechanism: first, are the effects due to changes in cortical or spinal excitability; second, are the effects caused by processes analogous to long term depression (LTD) or potentiation (LTP) as described in experiments on animal models?

Changes in spinal excitability may well occur with intensities of rTMS above threshold for evoking a descending corticospinal volley (usually around active motor threshold). Surprisingly, however, only two studies have addressed this question in detail. Valero-Cabré et al. (2001) applied 600 pulses of 1-Hz rTMS at 90% of resting motor threshold of the flexor carpi radialis (FCR) muscle and reported a lasting decrease in threshold and an increase in size of the FCR H-reflex. In contrast, Touge et al. (2001) found no effect of rTMS on the size of the FCR H-reflex after 600 stimuli at 1 Hz and 95% of resting motor threshold of the FDI muscle. It seems likely that the difference in results is due to differences in the intensity of the rTMS. Forearm flexor muscles have a higher resting threshold than the intrinsic hand muscles so that Valero-Cabré et al. (2001) may have used a higher intensity of rTMS than Touge et al. (2001).

In contrast to the spinal cord, there is good evidence for lasting effect on the cortex. For example, highfrequency subthreshold rTMS can reduce intracortical paired-pulse inhibition in the stimulated motor cortex (Pascual-Leone et al. 1998; Peinemann et al. 2000). Similarly, positron emission imaging (PET) studies have revealed a localized modulation of neural net activity within the stimulated primary sensorimotor cortex following subthreshold 5 Hz rTMS (Siebner et al. 2000).

The cellular mechanisms of the aftereffects are not yet clear. Studies with centrally acting drugs (see below) show that excitatory synaptic activity involving NMDA receptors is necessary to produce the aftereffects, implying that long term changes in synaptic transmission may be induced. However, other studies have shown that the aftereffects of motor cortex rTMS disappear if corticospinal excitability is tested in actively contracting muscles rather than at rest (Touge et al. 2001). The authors concluded that rTMS was most likely changing the level of excitability of the resting corticospinal system, rather than changing the effectiveness of transmission at synapses within the cortex. Perhaps both occur to a varying degree depending on the parameters of rTMS.

# Effects of rTMS at a distance from the coil

TMS can activate the output and input connections of any area of cortex. This means that the conditioning effects of rTMS are not necessarily limited to the cortical area targeted by rTMS but that changes could also occur at distant interconnected sites in the brain. Several studies have used physiological measures to reveal aftereffects of

rTMS at distant sites. Wassermann et al. (1998) reported that the corticospinal excitability of the motor cortex of one hemisphere is reduced after suprathreshold 1 Hz rTMS of the opposite hemisphere. Gerschlager et al. (2001) examined connections between the lateral premotor and primary motor cortex of the same hemisphere. They showed that stimulation of the lateral premotor cortex at 1 Hz rTMS and 90% active motor threshold decreased the size of MEPs evoked from the primary motor cortex for about 15 min (Fig. 2). This was not due to a spread of the rTMS to the primary motor cortex, since 1 Hz rTMS applied at 90% active MT applied directly over the primary motor hand area had no effect on corticospinal excitability. Munchau and colleagues extended this to show that a selective change in the motor cortex ICI/ICF curve could be produced by 1 Hz stimulation of premotor area at an intensity of 80% active motor threshold (Munchau et al. 2002).

These electrophysiological data are in agreement with functional imaging studies (Siebner et al. 2000; Paus et al. 2001; Strafella et al. 2001). Subthreshold 5 Hz rTMS of the left primary sensorimotor cortex (SM1) induced a lasting increase in regional glucose metabolism not only in the stimulated SM1 but also in the contralateral SM1 and the caudal supplementary motor area (Siebner et al. 2000). Using cerebral blood flow as an index of regional neuronal activity, Paus et al. (2001) provided evidence that 10 Hz rTMS over the mid-dorsolateral frontal cortex induced a lasting change in functional cortico-cortical connectivity of this region. In addition to lasting effects on cortico-cortical interactions, focal rTMS results also in a lasting modulation of cortico-subcortico-cortical reentry loops (Strafella et al. 2001). In healthy subjects, high-frequency rTMS of the left dorsolateral prefrontal cortex resulted in a reduction in [<sup>11</sup>C]raclopride binding in the left dorsal caudate, providing evidence for a lasting increase in endogenous dopamine release in the caudate nucleus. These distant effects of rTMS demonstrate that the conditioning effects of rTMS on the stimulated cortex may be seen as "the tip of the iceberg" and that distant conditioning effects (i.e. "network effects") need to be taken into account when using rTMS to induce representational plasticity.

Studies on the motor cortex indicate that the threshold for producing effects at a distance depends on the intensity of stimulation. The first elements to be activated are local inhibitory circuits whilst projection neurons are activated at higher intensities. Interestingly, neurons that project to different targets may also have different thresholds: for example, in the motor cortex hand area, corticospinal neurons appear to have a slightly lower threshold than transcallosally projecting neurons (Ferbert et al. 1992; Hanajima et al. 2001). As a result, the effects of rTMS may be limited to the stimulated area at very low intensities of stimulation but spread to dispersed interconnected areas at high intensities. In the latter case, it is even possible that the remote aftereffects outweigh the local effects under the coil.



**Fig. 2** Mapping the effect of 1 Hz rTMS at 90% active threshold on corticomotor responses evoked by a standard magnetic stimulus over the left motor hand area (modified with kind permission from Gerschlager et al. 2001). The *upper panel* illustrates the study design. Subthreshold 1 Hz rTMS was applied either over the motor hand area (as defined by the "hot spot" for TMS activation of hand muscles) or at points 2.5 cm anterior (lateral premotor cortex). Thirty MEPs were recorded at the beginning of each experiment (baseline). Ten MEPs were recorded immediately after each of the five 300-stimuli rTMS trains (*grey bars*) as well as 2, 5, 10, 15, 20, 25, and 30 min after the end of 1 Hz rTMS (*right panel*). The *lower* 

It is important to note that different subsets of neurons may be affected differentially by a given rTMS protocol. Thus, it may be the case that in some subsets of cortical neurons excitability is increased, whereas in others excitability may decrease or not change at all. One might also intuitively assume that an rTMS-induced net inhibition in the stimulated cortex equals a lasting rTMSinduced impairment in function. However, the relationship between lasting changes in excitability and lasting changes in functional properties is likely to be more complex.

A final consideration is that current spread to adjacent cortical areas is likely to occur when higher intensities of stimulation are used and activation of these structures may even be responsible for observed neuromodulatory effects. For instance, Gerschlager et al. (2001) put forward the hypothesis that suprathreshold 1 Hz rTMS applied over the primary motor hand area is likely to spread to the adjacent lateral premotor cortex which, in turn, may be responsible for the suppression of corticospinal excitability.

*panel* shows the effect of 1 Hz rTMS at 90% active threshold on the amplitude of MEPs evoked by a standard stimulus over the left motor hand area. Mean and standard deviation of the MEP amplitude of the right FDI muscles after 1, 2, 3, 4 and 5 trains of rTMS (*grey bars*); and 2, 5, 10, 15, 20, 25 and 30 min after the end of rTMS. Mean amplitudes are expressed as a percentage of mean amplitude before rTMS. Only 1 Hz rTMS over the left lateral premotor cortex induced a lasting reduction in corticomotor excitability probed by single magnetic stimuli over the left primary motor hand area (*arrow*)

Manipulating the aftereffects of rTMS

One of the practical problems of applying rTMS is the interindividual variability in the size and duration of the aftereffect. This has been documented most clearly for rTMS over the primary motor cortex (Maeda et al. 2000a, 2000b; Peinemann et al. 2000; Siebner et al. 2000), but is likely to be true for other areas. One possible problem is that most studies of rTMS have applied stimulation in subjects at rest. The lack of control over neuronal excitability in this relatively ill defined state may be one factor that contributes to the variability in the final response.

This idea is supported by work on healthy subjects showing that the conditioning effects of rTMS can be modified if cortical excitability is manipulated during application of rTMS. Several studies have focused on the combination of rTMS with interventions that manipulate sensory input to SM1 (Ziemann et al. 1998a; Stephan et al. 2000). Ziemann and colleagues (1998a) combined temporary ischaemic limb deafferentation (and deefferentation) with rTMS of the contralateral SM1. They used very slow rTMS (0.1 Hz) that had no aftereffects on motor excitability when applied alone. Ischaemic nerve block alone induced a moderate increase in MEP size in the biceps brachii muscle proximal to the level of deafferentation without any effect on paired-pulse inhibition or facilitation. However, the combination of ischaemic nerve block and 0.1 Hz rTMS over the SM1 contralateral to ischaemia significantly enhanced the facilitation of biceps MEP and also reduced paired-pulse inhibition, and increased paired-pulse facilitation. Interestingly, the combination of ischaemic nerve block and 0.1 Hz rTMS of the SM1 ipsilateral to the nerve block and 0.1 Hz rTMS of the SM1 ipsilateral to the nerve block induced an opposite pattern of excitability changes. The facilitation of MEPs was blocked, ICI became more pronounced, and paired-pulse facilitation was suppressed.

The conclusion from these studies is that temporary anaesthesia renders the corticospinal system susceptible to the conditioning effects of 0.1 Hz rTMS. Using the same plasticity model, Ziemann et al. (1998b) went on to show that CNS-active drugs such as the benzodiazepine lorazepam or the voltage-gated Na<sup>+</sup> and Ca<sup>2+</sup> channel blocker lamotrigine blocked rTMS-related upregulation of deafferentation-induced cortical plasticity, whereas the NMDA receptor blocker dextromorphan suppressed the decrease in paired-pulse inhibition only without affecting the increase in the MEP.

Instead of reducing the sensory input to SM1, Stefan et al. (2000) adopted an opposite strategy to manipulate the sensory input to SM1 during 0.1 Hz rTMS. They used a TMS intensity above resting threshold and paired it with a supra motor threshold electrical stimulus to the contralateral median nerve 25 ms before each TMS pulse. After 90 pairs of stimuli, there was a marked increase in corticospinal excitability that lasted a further 30 min or more. The duration of the postexcitatory silent period was also prolonged (Stefan et al. 2000). The effects occurred in all hand muscles, even those not innervated by the median nerve but not in biceps. The authors put forward the hypothesis that this form of plasticity was a form of associative long-term potentiation or a closely related mechanism.

Functional brain mapping of rTMS-induced reorganization

A variety of neuroimaging techniques are currently available to explore rTMS-induced cortical plasticity. One major advantage of combined TMS-neuroimaging studies is that functional neuroimaging picks up physiological signals which are directly generated in the brain and thus do not rely on indirect behavioural measures such as motor evoked responses or a disruption in task performance. The techniques can show whether rTMS affects the pattern of activity in the brain in the resting state or during performance of a task. In addition, they may be able to describe whether there is a change in the connectivity between brain areas.

#### EEG and MEG

Electroencephalography (EEG) and magnetoencephalography (MEG) can readily map changes in organization of cortical structures. However, deep sites, such as basal ganglia and thalamus, do not provide strong signals with these methods, and are best investigated with PET or fMRI (see below). Rossi et al. (2000) examined the pattern of brain activity associated with self-paced voluntary hand movements before and after 15 min of slightly suprathreshold 1 Hz rTMS over the SM1. Compared to sham-rTMS and a voluntary movement condition (which imitated the small twitch induced by rTMS), real-rTMS produced a significant amplitude decrement of the negative slope of the Bereitschaftspotential, providing evidence for a lasting interference of 1 Hz rTMS with movement-related cortical activity. Other authors have used coherence techniques to test how rTMS affects functional cortico-cortical connectivity. Jing and Takigawa (2000) gave two 3-s trains of threshold 10 Hz rTMS over the left prefrontal cortex, and found that this produced an increase in directed coherence between the stimulated area and parietal sites. They thought that rTMS had selectively reinforced connections from the stimulated site to other recording sites. Though no studies have yet been published, MEG may be particularly useful to map the time course and the regional pattern of changes in task-related cortex activity (e.g. changes in localization and orientation of distinct dipoles within a cortical area). In practical terms, MEG has the advantage that no surface electrodes need to be placed on the scalp that might interfere with application of rTMS. Indeed, it is relatively simple to record MEG shortly after a conditioning rTMS given outside the MEG room.

#### PET

Several reports have used positron emission tomography (PET) to investigate the regional pattern of lasting changes in net neuronal activity at "rest" by recording changes in the regional metabolic rate for glucose or the regional cerebral blood flow (rCBF). For instance, <sup>18</sup>FDG-PET provided evidence for an enduring increase in regional metabolic rate of glucose in the contralateral right SM1 and the caudal supplementary motor area after 2,250 pulses of subthreshold 5-Hz rTMS of the left SM1 (Siebner et al. 2000).

In contrast to <sup>18</sup>FDG-PET,  $H_2^{15}O$ -PET allows for repeated measurements (usually 12 subsequent scans) of net neuronal activity as indexed by rCBF. Thus,  $H_2^{15}O$ -PET allows imaging of both the regional pattern and the time course of functional plasticity induced by conditioning rTMS (Paus et al. 1997, 2001; Siebner et al. 2001). Siebner et al. (2001) applied a 30-s train of subthreshold 5-Hz rTMS to the left SM1. PET measurements of rCBF at rest revealed an increase in rCBF in the stimulated SM1 after a conditioning rTMS train that lasted for several minutes (Siebner et al. 2001). Patterns of functional connectivity can be measured in various ways using PET. One interesting approach is to use single (or double pulse) TMS to excite specific pathways. The effect on distant connected sites can then be quantified by measuring evoked changes in rCBF. Paus et al. (2001) used this method to test connections from/to mid dorsolateral frontal cortex before and after conditioning 10 Hz rTMS over the same area. The authors were able to demonstrate that conditioning rTMS caused a lasting change in cortical excitability of the cortical target area as well as changes in functional connectivity between the target area and distant brain regions.

In addition to studies of blood flow and glucose metabolism, PET offers the opportunity to investigate functional changes at a receptor level, using ligand-PET. Strafella et al. (2001) showed in a recent study that prefrontal rTMS results in an increase in raclopride binding in the ipsilateral anterior caudate nucleus, providing in vivo evidence for a remote functional change in the cortico-basal ganglia-thalamo-cortical loop after focal cortical rTMS.

#### fMRI

Compared with PET, functional magnetic resonance tomography (fMRI) using blood oxygenation level dependent (BOLD) contrast has a superior spatial and temporal resolution. Moreover, since fMRI does not involve radiation exposure, there are virtually no restrictions on the number of brain scans that can be acquired (Bohning et al. 1998, 1999). This allows for prolonged neuroimaging over several tens of minutes as well as for repeated fMRI measurements on separate days. Preliminary data suggest that fMRI is a sensitive tool to pick up task-related changes in BOLD contrast that are caused by conditioning rTMS (Pascual-Leone et al. 1998). In addition, statistical maps of relative changes in functional and effective connectivity between the cortical target of rTMS and interconnected brain regions can be used to characterize rTMS-induced changes in cortico-cortical and cortico-subcortical interactions. By recording task performance during fMRI, behavioural measures can be included as a regressor for fMRI data analysis. This will help to provide a closer link between changes in task performance (i.e. function) and modulations in neural activity (i.e. BOLD response) induced by rTMS. It is worth noting that rTMS and fMRI can be spatially and temporarily separated from each other when mapping the lasting functional effects of rTMS. If rTMS is applied outside the MRI room, no specific safety precautions need to be taken.

Considering the specific strengths and weaknesses of each neuroimaging tool, it is important to point out that the various modalities of functional imaging are complementary rather than being competitive. In fact, multimodal neuroimaging has the strongest investigative potential, since the specific drawbacks of a single imaging technique may be cancelled out by the specific advantage of a second imaging modality. For example, electrophysiological measurements of changes in motor cortical excitability may help to explain changes in rCBF or in the BOLD response.

Functional relevance of rTMS-induced plasticity

#### Healthy subjects

It is much more difficult to demonstrate behavioural effects of rTMS than it is to show changes in cortical excitability or functional cortico-cortical connectivity. One possible contributing factor is the finding in the motor cortex that prolonged changes in excitability are only seen in resting subjects and disappear when tested in the active state (Touge et al. 2001). Perhaps those behaviours that involve tasks going from rest to activity are more likely to be affected than those that involve continuous activity. Whatever the explanation, little change in overt movement behaviour is seen after 1 Hz rTMS over the SM1 (finger tapping speed, Chen et al. 1997; kinematics of handwriting movements, Siebner et al. 1999b; maximum pinch force or peak acceleration of brisk finger movements, Muellbacher et al. 2000) despite the fact that the same procedure can reduce corticospinal excitability when tested with TMS pulses. Intrinsically less variable measures, such as long latency stretch reflexes and somatosensory evoked potentials, are affected (Tsuji and Rothwell 2002), suggesting that part of the problem in detecting change lies in the intrinsic variability of volitional movements. It may also be that in many cases the motor tasks studied were highly overlearned and, thus, the motor system could easily compensate for TMS-induced alterations in cortex function. In accordance with this notion, a recent study by Muellbacher et al. (2002) showed that suprathreshold 1 Hz rTMS over the primary motor cortex caused a lasting interference with motor performance only at an early stage of motor learning but not after consolidation of a newly acquired manual motor skill. In addition, an aftereffect of rTMS on motor behaviour is more readily observed if more complex motor tasks are investigated (Pascual-Leone et al. 1998).

In contrast with the relative lack of behavioural effects on the motor system, several authors have described lasting effects of rTMS on cognitive functions in healthy volunteers (Kosslyn et al. 1999; Hilgetag et al. 2001). For instance, a 10-min train of 1-Hz rTMS over the ipsilateral parietal cortex improved spatial attention to ipsilateral targets (Hilgetag et al. 2001). The most plausible account for this finding is that parietal rTMS gave rise to a lasting modulation in interhemispheric competition in the distributed brain network for spatial attention (Hilgetag et al. 2001). Effects on mood have been described after rTMS of frontal cortex (Triggs et al. 1999), and improved analogic reasoning was seen after rTMS over left prefrontal cortex (Boroojerdi et al. 2001).

#### Neurological patients

A likely explanation for the difficulty in modifying behaviour consistently with rTMS in healthy subjects is that they can easily recruit additional brain areas to compensate for the effects of rTMS. As cortical function is a-priori impaired in patients, it may, in fact, be easier to demonstrate a behavioural consequence of rTMS in patients with a distinct neuropsychiatric disorder as opposed to healthy volunteers (Siebner et al. 1999a, 1999b).

The capacity of rTMS to temporarily alter brain function in the stimulated cortex opened up new possibilities to explore the role of distinct cortical areas in the pathophysiology of a specific disease (Siebner et al. 2002). However, the main clinical interest in rTMS has always centered around the question of whether or not rTMS can be used as a therapeutic tool. A number of studies have demonstrated that rTMS is capable of temporarily improving symptoms in a variety of neuropsychiatric diseases, including depression, epilepsy, and movement disorders (Pascual-Leone et al. 1996b; George et al. 1999; Siebner et al. 1999a, 1999b; Tergau et al. 1999). So far, the clinical improvement induced by rTMS has been modest, short-lasting and variable across patients. The area of greatest clinical interest has been the potential therapeutic use of rTMS over the prefrontal cortex in major depression (George et al. 1999). However, a recent meta-analysis on the therapeutic effects of prefrontal rTMS in depression came to the conclusion that "there is no strong evidence for benefit from using TMS to treat depression, although the sample size does not exclude the possibility of benefit" (Martin et al. 2002). Therefore, it is still unclear whether rTMS will emerge as a therapeutic option in neuropsychiatric diseases (George et al. 1999; Hasey 2001; Wassermann and Lisanby 2001; Siebner et al. 2002). The main problem is that the basic mechanisms mediating the beneficial effects of rTMS are still poorly understood (Siebner et al. 2002). Thus, given the biological heterogeneity across patients, there is currently no method at hand that enables us to fine-tune the parameters of stimulation to produce an optimum therapeutic effect in a given patient.

A common assumption is that modulatory effects in healthy subjects will help to predict therapeutic effects in patients. However, there is no real evidence to suggest that this is always the case. In analogy to experimental manipulation of the functional state of the cortex, the susceptibility to the conditioning effects of rTMS may well be different in patients as a consequence of their underlying pathophysiology. In support of this notion, a discrepancy between the conditioning effects of rTMS in patients and healthy controls has been demonstrated in patients with migraine and dystonia (Siebner et al. 1999c; Bohotin et al. 2002). For instance, a 30-min train of subthreshold 1-Hz rTMS over the SM1 caused a significant prolongation of the postexcitatory silent period and a reinforcement of intracortical paired-pulse inhibition in patients with writer's cramp but not in healthy controls (Siebner et al. 1999c). Since the excitability of inhibitory circuits is reduced in writer's cramp, these sets of neurons may be more susceptible to an rTMS-induced increase in excitability than in normal subjects (Siebner et al. 1999c). Accordingly, differences between patients and healthy subjects on corticomotor excitability have also been reported for immediate conditioning effects during the administration of rTMS (Siebner et al. 1999d).

#### Animal studies of rTMS-induced plasticity

Since rTMS is a tool that can be used to explore cortical reorganization at a regional level, it remains a challenge to link the patterns of cortical plasticity revealed by TMS to changes at a neuronal level. Only a limited number of animal studies on the basic mechanisms of rTMS-induced plasticity have been conducted so far. Nonetheless, the published animal data indicate that rTMS results in a lasting modulation of brain function at the molecular and cellular level. In the rat brain, there is a regionally specific increase in the expression of immediate early genes (Fujiki and Steward 1997; Hausmann et al. 2000; Ji et al. 1998) and brain-derived neurotrophic factor (Muller et al. 2000) in response to rTMS and there is some evidence for a neuroprotective effect of rTMS (Post et al. 1999). In rodents, rTMS exerted modulatory effects on monamine neurotransmitter systems (Ben-Shachar et al. 1997; Keck et al. 2000a). Moreover, chronic rTMS induced sprouting of mossy fibres in the hippocampus.

In human TMS studies on motor cortical plasticity, lasting changes in synaptic efficacy, in particular longterm depression and potentiation (LTP and LTD), have been proposed as mechanisms that underlie the observed changes in cortical excitability. In support of this notion, high-frequency rTMS has been shown to concurrently induce LTP-like and LTD-like mechanisms in rodent auditory cortex (Wang et al. 1996). Another in vivo item of evidence for lasting changes in neuronal excitability was observed in the hippocampus of the anaesthetized rat (Levkovitz et al. 1999). Application of non-focal rTMS resulted in a long lasting (for at least 3 weeks) decrease in paired-pulse inhibition and an increase in paired-pulse potentiation in response to paired-pulse stimulation of its main excitatory afferent pathway. In addition to this excitatory effect, rTMS concurrently caused a large and prolonged suppression of the reactivity of the hippocampus to the serotonin-releasing drug fenfluramine (Levkovitz et al. 1999).

Due to the small brain volume, focal rTMS is technically difficult to achieve in rodents and thus the effect of rTMS was considerably more widespread than in humans. Indeed, one has to assume that most parts of the brain were effectively stimulated by rTMS in most of the animal studies. These differences in the effectively stimulated brain volume render it difficult to transfer the existing animal data to human work on rTMS. Moreover, it is conceivable that at least some of the functional changes demonstrated in animals were due to the considerable amount of repetitive physiologic sensory stimulation caused by direct stimulation of peripheral nerves and TMS-induced movements. It is worth noting that magnetic stimulation of rodent brains is not diffuse by necessity. One possibility of working around these problems is to calculate the spatial distribution of current density induced in the rat and human brain and to adjust the stimulation parameters according to these calculations (Keck et al. 2000b).

Though there are many caveats when trying to relate modulatory effects of rTMS on synaptic transmission in the rodent brain to rTMS effects in the human cortex, these animal data clearly show (1) that rTMS is capable of inducing long lasting changes in synaptic transmission of cortical synapses, neurotransmitter systems, and gene expression and (2) that the pattern of induced changes is highly complex, simultaneously involving inhibitory and facilitatory effects. Since rTMS interacts with the stimulated cortex in an immensely complex fashion, it is unlikely that a distinct conditioning effect of rTMS on cortex function is attributable to a single underlying mechanism. The lasting cellular and molecular effects of rTMS in animals, especially in non-human primates, warrants further detailed study to allow a better interpretation of the modulatory effects of rTMS on the human cortex in terms of the underlying molecular and synaptic mechanisms.

# Conclusion

During the last decade, TMS has emerged as a powerful tool to investigate representational plasticity of the human cortex. It has been used most extensively in the corticospinal system, since motor evoked responses are convenient means to assess changes in corticospinal excitability, but development of behavioural tests has made it possible to apply TMS to a variety of cognitive processes.

The potential of rTMS to cause lasting effects on cortical function makes it a unique technique to interfere actively with cortical plasticity in intact humans. It is anticipated that the combination of rTMS with welldefined interventions (e.g. sensory stimulation, premedication, task performance) will provide powerful in vivo models that are useful to elucidate the underlying mechanisms of cortical reorganization. By selecting an appropriate rTMS protocol, it may be possible to determine the direction, to prolong the duration, and to finetune the magnitude of the modulatory effects of rTMS. Stimulation techniques that allow cortical plasticity to be modulated in a predictable fashion may eventually have a therapeutic implication in patients, since they could be used actively to "manipulate" cortical reorganization. On one hand, scientifically based rTMS protocols may be used as a therapeutic means to actively suppress the mechanisms which mediate "maladaptive" plasticity, leading to a deterioration of brain function (e.g. poststroke dystonia or phantom limb pain). On the other hand, rTMS may be of value in enhancing "beneficial" plasticity (e.g. motor recovery after stroke). However, we still need to know a good deal more about the basic mechanisms that mediate the modulatory effects of rTMS in patients before rTMS can be seriously considered as a therapeutic option.

Recent efforts to combine TMS with modern brain mapping techniques have considerably expanded the applications of TMS in neuroplasticity research. In contrast to electrophysiology, tomographic imaging techniques allow us to assess the conditioning effects of rTMS throughout the entire brain, including rTMS-associated interactions between the stimulated cortex and interconnected brain regions. Particularly exciting is the possibility of imaging changes in receptor function together with effects on metabolic activity. The combination of TMS with other stimulation techniques, such as peripheral electric (magnetic) nerve stimulation or transcranial direct current stimulation, will further extend the possibilities of investigating the mechanisms which mediate functional reorganization in the human brain (Stefan et al. 2000; Nitsche and Paulus 2000).

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