Robert Chen · John C. Rothwell *Editors*

Cortical Connectivity

Brain Stimulation for Assessing and Modulating Cortical Connectivity and Function

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Preface

As brain science evolved from defining and studying the workings of individual brain areas to the study of brain networks, there is increasing interest in the way different areas of the brain interact with each other and how these interactions change while subjects perform different tasks or learn new skills. Key studies in non-human primates have greatly advanced our knowledge in this area. Exciting new tools are now available to study the operation and formation of these networks in the human brain in health and disease. These include neuroimaging measures of functional connectivity, magnetoencephalographic and electroencephalographic studies and new methods of transcranial brain stimulation. These methods provide unique ways to probe individual connections and interactions within a complex system.

This book is an outcome of a minisymposium entitled "Functional modulation of the primary motor cortex: from animal models to clinical applications" held at the Society for Neuroscience meeting in San Diego in November 2010. We expanded the topics discussed at the minisymposium and included additional authors who are leaders in the field. The chapters are organised into three parts: the first deals with studies in primates; chapters in the second section describe how it is possible to use non-invasive tools to probe and manipulate connectivity in healthy individuals; the last section then considers the changes in connectivity in neurological and psychiatric disease.

The aim of the book is to bring an up-to-date perspective on new methodologies that are increasingly being used not only to probe, but even to modulate the excitability of cortical connections in animal and in human brain. These studies have advanced our understanding of the normal function of the brain circuits studied, but also form the basis for new therapeutic applications in neurological and psychiatric disorders.

Robert Chen
John C. Rothwell

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Chapter 1
Plasticity in Motor Cortical Connectivity

Andrew Jackson

Abstract After a brief overview of the anatomical and functional organisation of the corticospinal system, this chapter will review the extensive evidence for the reorganisation of primary motor cortical connectivity during motor learning. Acquisition of new skills results in an expansion of the cortical representation of trained limbs that is underpinned by synaptic plasticity in intracortical and spinal circuits. Three stimulation protocols will be introduced which can be used to induce similar plastic changes artificially according to Hebbian principles. I will examine how these protocols relate to the mechanisms of skill learning and suggest opportunities for their application in the rehabilitation of movement following nervous system injury.

1.1 Introduction

Is brain function best understood in terms of localised computation performed by specialised areas or as distributed representations spread across interconnected networks? This question has played a central role in the development of modern neuroscience, from the nineteenth century debates between Goltz and Ferrier over the effects of selective cortical ablations (Phillips et al. 1984) to Lashley's search for the elusive 'engram' (Lashley 1950) and Hebb's conception of the cell assembly (Hebb 1949). The second half of the twentieth century saw neuroscientists make great progress analysing the specialised cortical regions revealed by human functional imaging studies and exploring specific stimulus features encoded by single

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neurons recorded in awake, behaving animals. Yet, recent technological and methodological advances have once again pushed the study of distributed, interconnected networks to the fore. Multi-electrode arrays and in vivo optical imaging now allow the activity of large-scale neuronal populations to be monitored in behaving animals, while new analysis methods are revealing correlated networks of brain regions in human imaging data. High-throughput microscopy and MRI-based tractography techniques pave the way toward mapping entire 'connectomes' and examining how they are modified by experience. Finally, the ability to alter the strength of connections using invasive or non-invasive stimulation protocols is providing new clinical opportunities to manipulate connectivity and restore function after disease or injury.

This chapter will focus on the primary motor cortex (M1) and the descending corticospinal pathway, and will draw predominantly on insights from animal studies. This corticospinal system has several advantages for the study of connectivity and its relationship to brain function. First, the anatomical substrates are relatively well understood and the output, in terms of muscle activation and movement, can be precisely quantified. Second, the control of movement requires multiple effector muscles acting at different joints to be coordinated into purposeful, goal-driven behaviours. We should, therefore, not be surprised to find that movement representations are distributed across a rich, interconnected network. Third, our ability to adapt behaviour and acquire new motor skills such as tool-use is surely one of the brain's most remarkable attributes and is central to our evolution as a species. Finally, disorders of the motor system are amongst the most debilitating neurological conditions, but an understanding of the mechanisms that modify connectivity within motor networks raises the hope of developing of novel therapeutic approaches.

1.2 Structural and Functional Connectivity in the Corticospinal System

1.2.1 Organisation of Descending Connections

Among the descending pathways involved in the control of movement, the corticospinal system is of particular importance for voluntary, goal-driven actions in primates including man. Heffner and Masterton (1975) found digital dexterity across species to be well correlated with the number and extent of corticospinal projections, and their terminal distribution within the spinal cord is characterised by increased projections to ventral motoneuron territory in the Old World primate (Kuypers 1981). The significance of this pathway for the fine control of the hand is supported by the profound deficits that result from lesion of the pyramids (Lawrence and Kuypers 1968). The frontal and parietal areas of the cerebral cortex that contribute to the corticospinal projection comprise a network of reciprocally

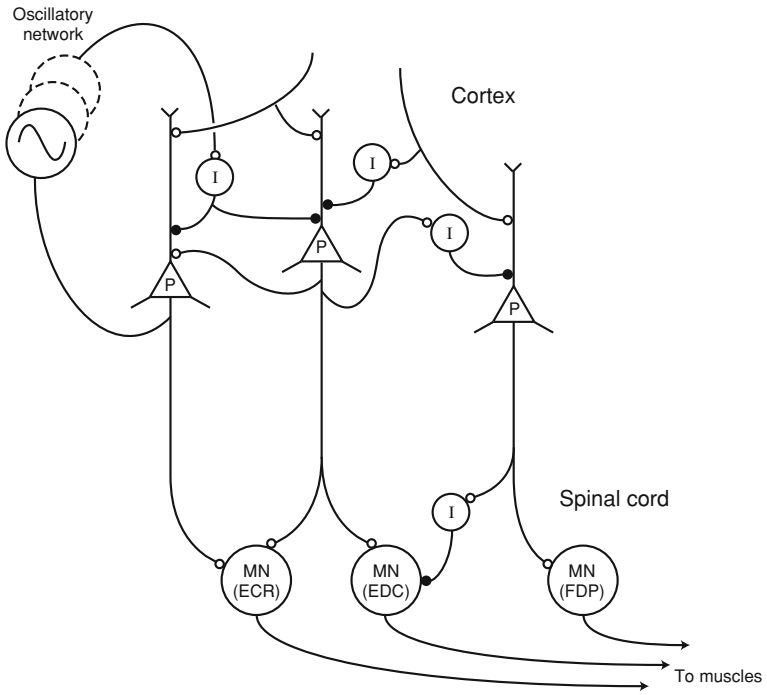

Fig. 1.1 Schematic of some of the known connections in the corticospinal system. Many layer V pyramidal neurons (P) make direct CM connections to motoneurons (MN) in the spinal cord. CM cells with overlapping muscle fields are synchronised by common inputs and recurrent excitation (e.g. Cell 1 and Cell 2 in Fig. 1.2). Cells with opposing (facilitation vs. suppression) effects in the same muscles are mutually inhibited by interneurons (I). In addition, CM cells are embedded within recurrent networks with beta-frequency rhythmicity

interconnected regions. But while it has been argued that these may reflect a parallel rather than hierarchical organisation (Dum and Strick 2002), M1 undoubtedly makes the largest contribution to the corticospinal pathway in terms of both number and diameter of fibres. Approximately, 10–20 % of M1 pyramidal cells in layer V project via the pyramids to the spinal cord where many make monosynaptic cortico-motoneuronal (CM) connections (Fig. 1.1).

Early mapping of M1 output using surface stimulation in monkeys (Woolsey et al. 1952) and man (Penfield and Jasper 1954) revealed a somatotopic representation of the body with movements of feet and legs elicited from medial areas, progressing laterally to arm, hand and face areas. However, more precise maps derived from intracortical microstimulation (ICMS) have revealed a 'fractured somatotopy' within this gross organisation, such that individual movements are represented in a patchwork of multiple, interspersed fragments (reviewed by Schieber 2001). It is important to note that ICMS does not necessarily reveal the underlying organisation of the CM cells since distant neurons can be activated indirectly via passing axons (Jankowska et al. 1975; Asanuma et al. 1976; Cheney

and Fetz 1985). Two-photon calcium imaging reveals that sparse populations of neurons respond to stimulation, sometimes several millimetres away from the electrode (Histed et al. 2009). Therefore, it was possible that the distributed ICMS maps obscured an orderly arrangement of the CM cells projecting to each muscle. However, retrograde labelling using transneuronal transport of rabies virus from forearm muscles has now verified the broad distribution of CM cell colonies in the anterior bank of the central sulcus, with extensive overlap of the projections to different muscles (Rathelot and Strick 2006). Interestingly, while ICMS effects are generally consistent with the CM cell territories in this caudal part of M1, there are few CM cells located in the convexity of M1 where low threshold ICMS responses can, nevertheless, be elicited (Rathelot and Strick 2009). Whether these responses are mediated via intracortical projections to CM cells, or by descending oligosynaptic pathways to motoneurons remains to be determined.

The convergence of cortical output from broad territories of motor cortex onto the spinal cord is mirrored by divergent projections of individual CM cells to multiple muscles. Corticospinal axons exhibit considerable branching at the spinal level, such that a single cell may contact many motoneurons (Shinoda et al. 1981; Lawrence et al. 1985). The extent of effective CM projections from a single cell is revealed in the awake monkey by compiling spike-triggered averages of the muscle electromyogram (Fetz and Cheney 1980; Jackson et al. 2003). Post-spike facilitation at latencies consistent with monosynaptic CM excitation is observed, typically in 2–3 different muscles but sometimes many more (Fig. 1.2a). Often spike-triggered averages reveal post-spike suppression of other muscles at a slightly longer latency, presumably mediated by a disynaptic pathway via inhibitory spinal interneurons. While the CM projection is generally strongest to hand muscles, cells with muscle fields that span distal and proximal joints have also been reported (McKiernan et al. 1998). These projections likely provide the motor cortex with a rich anatomical substrate by which to control coordinated arm and hand movements.

1.2.2 Organisation of Intracortical Connections

In addition to their descending projections to the spinal cord and brainstem, pyramidal neurons in motor cortex make horizontal connections via intracortical axon collaterals (Ghosh and Porter 1988). Typically, three to five collaterals arborize predominantly in laminate V and VI to target other pyramidal neurons and a variety of intracortical inhibitory interneurons (Fig. 1.1). These connections span considerable distances within M1; labelling from a horseradish peroxidase injection at a site in the thumb representation extends across the entire forelimb area of M1 (Huntley and Jones 1991). The effects of this recurrent intracortical connectivity are revealed by activating corticospinal axon collaterals by pyramidal tract stimulation, which produces both excitation and inhibition of pyramidal neurons at short latency (Jackson et al. 2002; Fig. 1.3c). Later cycles of suppression and facilitation reflect

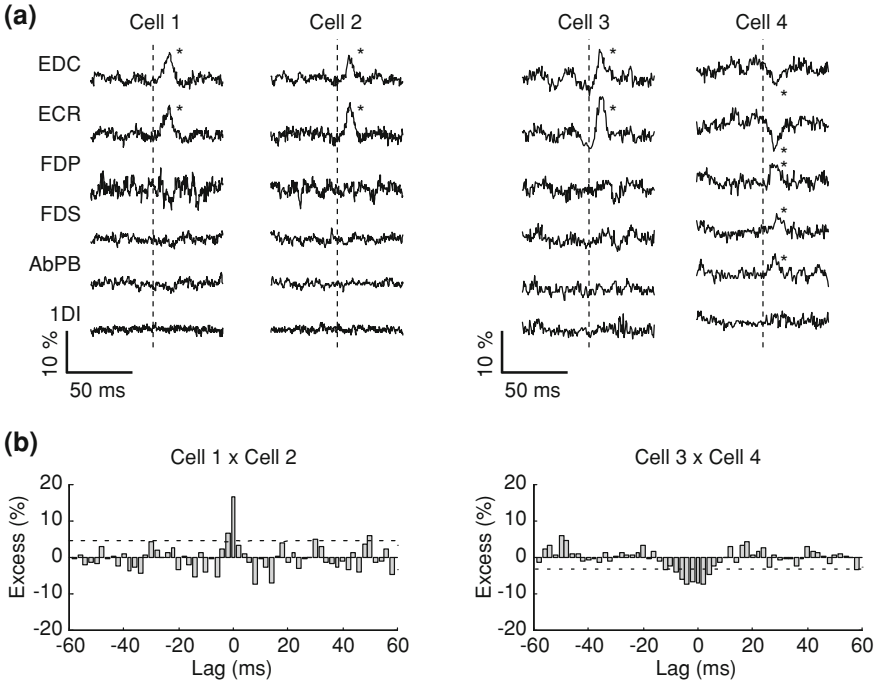

Fig. 1.2 Relationship between synchrony and muscle field overlap. **a** Spike-triggered averages of rectified electromyogram activity during grasping movements reveal the muscle fields of CM cells. Significant post-spike facilitation (consistent with monosynaptic excitation of motoneurons) and post-spike suppression (indicative of disynaptic inhibition) are indicated (*). **b** Cross-correlation histograms reveal that synchrony between CM cells depends on the degree of muscle field overlap. Cells 1 and 2 have similar muscle fields and exhibit a cross-correlation peak. Cells 3 and 4 have opposing effects in muscles EDC and ECR, and show a cross-correlation trough. Adapted from Jackson et al. (2003)

the influence of beta-frequency oscillations that are phase reset by stimulation (Fig. 1.3a, b) suggesting CM cells are embedded within large, recurrent networks exhibiting rhythmical characteristics.

Multi-electrode recording in awake primates has revealed synchronous action potential discharge between pairs of CM cells separated by up to a millimetre (Jackson et al. 2003). Interestingly, synchrony is greatest amongst CM cells with overlapping muscle fields (i.e., when both cells facilitate a similar set of muscles), even though the firing rate of these cells can have very different relationships to a movement (Fig. 1.2b). CM cells with opposing effects (facilitation vs. suppression) in the same muscles predominantly exhibit a cross-correlation trough. Thus, the organisation of the synaptic connections mediating synchrony between CM cells seems to reflect their output connectivity at the level of muscles (Fig. 1.1).

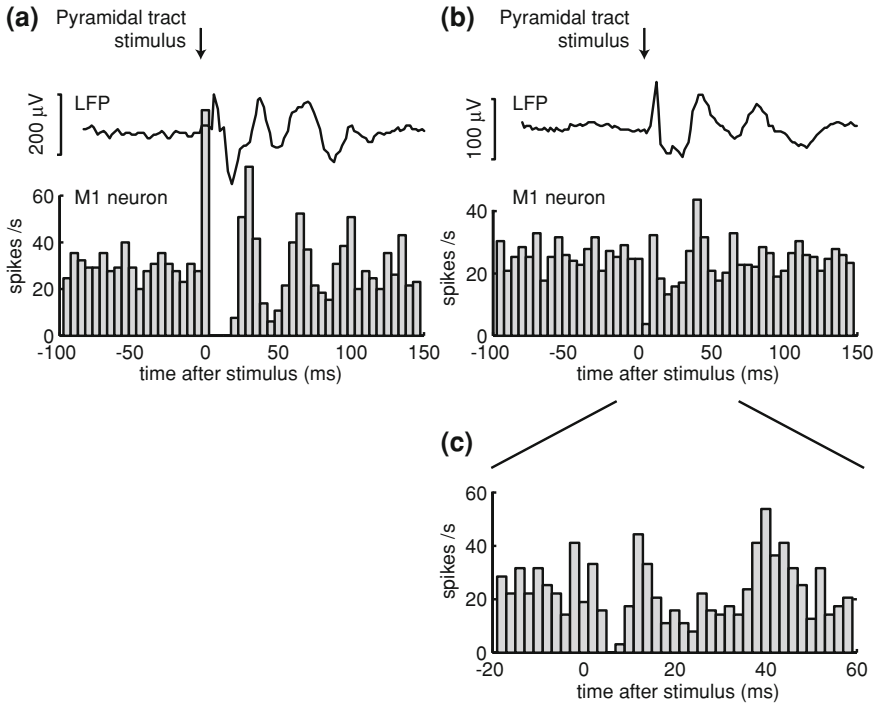

Fig. 1.3 Corticospinal neurons in motor cortex are embedded within recurrent, oscillatory networks. **a** Stimulation of the pyramidal tract antidromically activates motor cortical neurons with descending projections. The peri-stimulus time histogram reveals the antidromic response, followed by rhythmical firing. Stimulus-triggered average of the local field potential (LFP) indicates that the cell is locked to a global beta-frequency oscillation that has been phase reset by the stimulus. **b** This cell does not exhibit an antidromic response (although stimulation at a higher current revealed a descending projection, not shown). However, the cell nevertheless becomes entrained to the reset global oscillation. **c** Close up of peri-stimulus time histogram reveals short-latency recurrent inhibition from pyramidal tract stimulation. Adapted from Jackson et al. (2002)

1.3 Plasticity in the Corticospinal System During Skill Learning

1.3.1 Skill Learning Induces Cortical Map Plasticity

The idea that cortical motor maps are dynamic can be traced back to Brown and Sherrington (1912) who investigated the 'instability of a cortical point'. Noting that responses to cortical stimulation seemed more variable than spinal or decerebrate reflexes they suggested that such instability may reflect 'one of the specific offices of the cerebral cortex' (p. 277). We now know that motor learning is associated with a long-term reorganisation of specific movement representations in the cortex. In monkeys, repeated practise of a skilled finger movement (retrieving

pellets from a small well) over several weeks resulted in an expansion of the area of M1 from which movements of the digits could be elicited by ICMS (Nudo et al. 1996). This effect was not due simply to increased use since extensive repetition of a simpler task (retrieving pellets from a large well) did not produce task-related map reorganisation (Plautz et al. 2000). The expansion of cortical territory is specific to the body part trained; acquiring proficiency at a wrist pronation/supination task resulted in an expansion of the wrist area of M1 (Nudo et al. 1996). These observations, which have been corroborated in rodents (Kleim et al. 1998) as well as humans (Pascual-Leone et al. 1995), suggest a straightforward relationship between cortical map area and dexterity. However, this simple explanation is complicated by the different time course of skill learning and map reorganisation (Kleim et al. 2004) with increases in cortical area occurring only during the late stages of training. Therefore, the reorganisation of motor maps may reflect the consolidation of a skill rather than its acquisition. This interpretation is supported by recent human experiments suggesting that non-invasive stimulation of M1 predominantly affects retention rather than acquisition of motor skills (Hadipour-Niktarash et al. 2007; Reis et al. 2009; Galea et al. 2011).

1.3.2 Skill Learning Alters Intracortical Connections

As noted earlier, movement responses to ICMS involve indirect activation of corticospinal neurons by intracortical axons. It therefore seems likely that the expansion of motor cortical maps following learning reflects, at least in part, plastic changes in the efficacy of these horizontal pathways leading to an increased territory from which neurons with descending outputs can be activated. Evidence for this was supplied by Rioult-Pedotti et al. (1998) who examined the strength of intracortical connections in layer II/III of rats trained on a food retrieval task. In brain slices taken shortly after training, the amplitude of local field responses to stimulation (at a second site) was enhanced in the motor cortex contralateral to the trained limb compared to the control hemisphere. Monfils and Teskey (2004) used chronically implanted stimulating electrodes in the corpus callosum to examine cortical evoked potentials at different stages of training. They reported enhanced responses in the trained hemisphere in the period during skill acquisition, corresponding to the period of map reorganisation (Kleim et al. 2004). This is preceded by increased *c-fos* expression and synaptogenesis (Kleim et al. 1996), and appears dependent on local cholinergic input from the basal forebrain (Conner et al. 2003, 2010).

The recent development of time-lapse imaging of dendritic structure in vivo using two-photon microscopy has provided new insights into the mechanisms of motor learning and map reorganisation. The formation and elimination of spines on the dendrites of layer V neurons in mice is a dynamic process that persists to an extent into adulthood. A transient increase in the rate of formation leads to an increase in spine density during the acquisition phase of skill learning (Xu et al. 2009), corresponding to the period of enhanced evoked potentials found by

Monfils and Teskey (2004). A subsequent increase in the rate of spine elimination leads to an ultimate spine density equal to untrained animals. However, the new spines are more stable than those formed spontaneously under control conditions. Moreover, most persist during subsequent learning of a second task, suggesting that different motor behaviours are stored by distinct sets of synapses. An interesting question that remains unanswered is whether the increase in spine formation observed during skill acquisition reflects a higher proportion of new spines being stabilised by the familiar mechanisms of synaptic potentiation, or whether another signalling process directs neurons to generate spines at a higher rate. Also, it is not clear whether spines form spontaneously in a random fashion or are guided by intrinsic or activity-dependent processes (Shen and Cowan 2010). Nevertheless, it seems that while most new spines forming under control conditions are unstable and subsequently eliminated, this dynamic process provides resources for the development of stable synaptic connections between appropriate neurons when learning takes place.

1.3.3 Skill Learning Alters Neuronal Correlations

Perhaps due to the technical difficulty of recording action potentials from the same population of neurons over long periods of time, as yet there is a paucity of evidence that reorganisation of motor maps and horizontal connectivity is associated with altered correlations in neuronal discharge. Schieber (2002) reported that monkeys trained for over 5 years on a complex finger movement task showed enhancement of the broad facilitation in spike-triggered EMG averages that are indicative of high synchrony between CM cells. The ratio of such effects to pure post-spike facilitation was greater in these highly trained animals than in a monkey that had performed the task for less than 1 year. These results are consistent with a training-related increase in the strength of the intracortical connections that synchronise CM cells with overlapping muscle fields (Jackson et al. 2003). However, this finding should be interpreted with caution since there is substantial variability in the prevalence of synchrony between individuals. Kilavik et al. (2009) observed long-term changes in motor cortex synchrony after learning a task that involved estimation of elapsed time. Monkeys moved to one of two targets according to whether a cue was presented after a short or long delay. After training, the rate of synchronous firing, or 'unitary events', was elevated at the time point corresponding to the short delay, even when the cue did not appear. When trained with a new time delay, this elevated synchrony shifted over weeks to reflect motor preparation at the time of the new delay. Finally, a recent study by Komiyama et al. (2010) used calcium imaging in mice learning to associate odor cues with licking responses. They reported an increase in the correlation between neighbouring neurons that encoded a similar motor response, consistent with a strengthening of intracortical connections between sub-networks of functionally related neurons. However, the poor temporal resolution of calcium imaging makes

it hard to relate these results directly to the shorter time-scale correlations observed in multi-electrode recordings.

The advent of chronic electrode arrays that allow large populations of neurons to be stably recorded from multiple brain regions over consecutive days promises to reveal further insights into how plasticity in intracortical connectivity reshapes distributed neural activity during learning. One field, which has led the way in exploiting these techniques, is that of Brain-Machine Interfaces (BMIs). In BMI experiments, the activity of multiple motor cortex neurons is decoded in real time and used to control the movements of a computer cursor or robotic effector (Taylor et al. 2002; Carmena et al. 2003). While early experiments aimed to develop decoders that mimicked the normal relationship between neurons and natural movements, it was, nevertheless, noted that widespread changes in neuronal tuning functions were observed during 'brain control'. More recent experiments have shown that monkeys can learn to control multiple decoders, and switch quickly between them (Ganguly and Carmena 2009). Learning to control a BMI involves a reorganisation of the relationships between neurons. For example, Carmena et al. (2003) reported the emergence of groups of neurons sharing similar directional tuning. Similarly tuned neurons exhibit similar patterns of phase coupling to beta-frequency local field potentials (Canolty et al. 2010) suggesting they form large scale, distributed functional assemblies coupled by oscillatory activity. Furthermore, the firing rate modulation of neurons which do not directly control BMI movements is reduced as the population activity is progressively optimised to the new control mode (Ganguly et al. 2011; Jackson and Fetz 2011).

1.3.4 Plasticity in Spinal Circuitry

While most studies of skill learning have focused on the cortex, it should be recognised that plasticity of descending projections and spinal circuitry may also contribute. Certainly, activity-dependent plasticity is vital for the correct development of the corticospinal system (Martin et al. 1999) and there is evidence that spinal circuits can be modified by experience through adulthood. Meyer-Lohmann et al. (1986) found that in monkeys trained for about 3 years on a task that involved resisting sudden perturbations, short-latency spinal stretch reflexes were gradually enhanced, while longer latency responses were abolished. Similar changes in H-reflex magnitude can be observed in human subjects after training on a new motor skill, e.g. backwards walking (Schneider and Capaday 2003). More rapid changes in reflex magnitudes can be achieved by operant conditioning techniques (Wolpaw et al. 1983). However, there is evidence for differential effects at cortical and spinal levels of skill versus strength training. Rats trained on a 'power reaching' task that required increased forelimb skill and strength showed comparable map reorganisation to animals trained on skill alone, but there was also an increase in the number of excitatory synapses onto motoneurons of the strength-trained animals (Remple et al. 2001; Adkins et al. 2006). This dissociation is corroborated by human studies;

while training on piano sequences results in a larger cortical representation of the digits (Pascual-Leone et al. 1995), resistance training produces plasticity predominantly at the spinal level (Carroll et al. 2002).

1.4 Techniques for Inducing Plasticity in the Corticospinal System

1.4.1 Hebb's Rule of Associative Plasticity

The studies of skill learning reviewed in the previous section suggest that motor map reorganisation is due, at least in part, to plasticity in horizontal pathways within the motor cortex. If so, then it is reasonable to ask whether such plasticity can also be induced by artificial stimulation protocols. The mechanism by which neuronal activity is thought to drive cortical plasticity is often credited to the psychologist Donald Hebb (although his ideas were anticipated in earlier writings of Herbert Spencer and William James). Hebb (1949) proposed that some 'growth process or metabolic change' (p. 50) occurs to strengthen the connectivity between two neurons when there is a consistent causal relationship between their activity. This mechanism is commonly summarised by the phrase 'cells that fire together wire together' and is now understood to occur due to NMDA receptor-mediated synaptic potentiation. Three stimulation paradigms have been used to impose this Hebbian condition artificially on neurons in order to induce synaptic plasticity (Fig. 1.4).

1.4.2 Repetitive Stimulation

Strongly tetanic stimulation of a single pathway is commonly used to produce correlated pre- and post-synaptic activity leading to long-term potentiation (LTP) of synapses. Trains of ICMS delivered to sensory cortex enhanced the amplitude of evoked excitatory post-synaptic potentials (EPSPs) in motor cortex neurons (Sakamoto et al. 1987). As with hippocampal LTP (Bliss and Lomo 1973), the effect was specific to the tetanised pathway since EPSPs evoked from a second site in sensory cortex were unchanged. Using a slightly unusual stimulation protocol, Nudo et al. (1990) found that low frequency (1 Hz) repetitive stimulation delivered for several hours to the rat motor cortex caused an expansion of the movement representation at the stimulated site. Similar map expansion has since been observed after tetanic stimulation of the corpus callosum (Monfils et al. 2004).

These studies show that in vivo repetitive stimulation protocols can produce many of the same changes in motor cortex connectivity that are also observed with

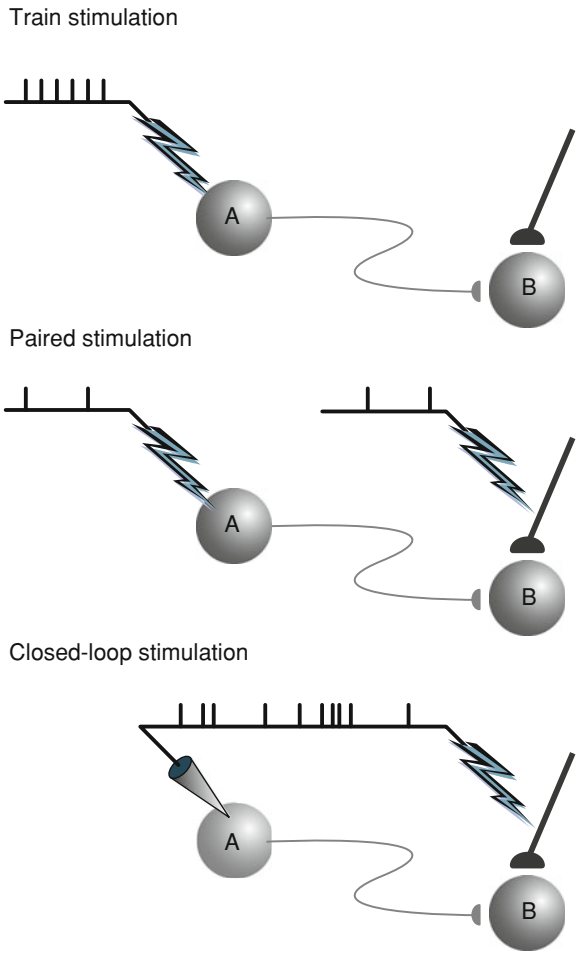

Fig. 1.4 Three protocols for inducing plasticity in the connection between cell A and cell B according to Hebb's rule. Train stimulation induces correlated pre- and post-synaptic activity by strong activation of a single pathway. Alternatively, single stimuli that activate cell A can be paired with stimulation of a strong input to cell B. Finally, closed-loop stimulation uses endogenous activity recorded from cell A to trigger stimulation of cell B

skill learning, but provide only indirect evidence of a common underlying mechanism. The first demonstration of a direct link between skill learning and motor cortex LTP was provided by Rioult-Pedotti et al. (2000) who examined whether prior training of rats to perform a reaching task influenced the subsequent artificial induction of plasticity of horizontal connections. Interestingly, forelimb training reduced the amount of LTP that could be induced in the contralateral hemisphere, while long-term depression (LTD) produced by low-frequency stimulation was enhanced. This suggests that synapses had been strengthened during learning up to a ceiling beyond which no further potentiation could be induced. When tested 2 months after initial learning, horizontal connections remained enhanced, but the normal range of potentiation and depression was restored (Rioult-Pedotti et al. 2007). These results point to homeostatic metaplasticity mechanism acting to maintain synapses within a working range,

possibly supported by post-synaptic receptor trafficking (Perez-Otano and Ehlers 2005), structural plasticity (Nimchinsky et al. 2002) and the formation of new spines (Xu et al. 2009).

1.4.3 Paired Stimulation

An early study by Baranyi and Feher (1981) found that stimulus-evoked EPSPs in cat motor cortex were facilitated if they were repeatedly paired with a stimulus delivered to a second input that was sufficiently strong to evoke an action potential within a time window of approximately 100 ms. Facilitation was reported to occur irrespective of whether the EPSP preceded or followed the spike. This appears to be in contradiction to later observations of spike-timing-dependent plasticity (STDP) in cortical slices (Markram et al. 1997); while synaptic inputs that precede action potentials were potentiated, synapses activated following action potentials were depressed. In this way, STDP appears appropriate as a Hebbian mechanism to strengthen *causal* connections between neurons. The STDP mechanism is believed to underlie the effect of paired associative stimulation (PAS) in humans (Stefan et al. 2000) in which transcranial magnetic stimulation (TMS) of motor cortex is timed relative to a somatosensory evoked potential produced by peripheral nerve stimulation. If TMS is repetitively delivered after the arrival of the sensory volley, repeated pairing leads to an enhancement of motor cortical excitability as measured by the muscle response to a test TMS pulse. On the other hand, TMS stimuli that precede sensory inputs result in reduced cortical excitability.

Rebesco and Miller (2011) have recently developed a paired stimulation approach using multiple electrodes implanted in the sensorimotor cortex of rats. The rats were first trained to respond to ICMS delivered to the electrodes by pressing a lever. Over a period of several days, trains of stimuli were delivered to pairs of electrodes with interstimulus intervals of 5 or 100 ms. Functional connectivity between neurons recorded at each electrode was inferred from the parameters of a generalised linear model fitted to spontaneous spike activity. After stimulation with the 5 ms interval, functional connectivity between stimulated electrodes was increased, while there was no net change in non-targeted electrodes. Interestingly, it was also possible to demonstrate a behavioural effect of the stimulation protocol; the rat's ICMS-detection threshold was subsequently reduced. The behavioural changes had a similar time course to the changes in cortical connectivity.

1.4.4 Closed-Loop Stimulation

Both tetanic trains and intermittent pairing represent highly artificial stimulation protocols that do not reflect the complex temporal structure of natural activity in neuronal networks. Recently, a new approach was introduced using spontaneous activity recorded at one site to control stimulation of a second site (Jackson et al. 2006a). These experiments exploited an autonomous electronic implant, or 'Neurochip', developed to perform long-term neural recording and stimulating in freely behaving monkeys (Mavoori et al. 2005). Over a continuous period of several days and nights, individual action potentials recorded from one electrode in the wrist area of M1 continually triggered single stimuli delivered to a second site. This protocol produced a lasting shift in the movement representation at the recording site; the direction of wrist movements evoked by ICMS shifted toward those evoked from the stimulation site (Fig. 1.5). These changes persisted in some cases for up to a week, although in other cases reversed gradually over subsequent days. Altered motor output resulted only when stimuli were delivered within $\sim$50 ms of the triggering spike and were restricted to the recording electrode; ICMS effects from other control electrodes were unchanged. It seems unlikely that this reorganisation can be accounted for by plasticity in the projections of the recorded neuron alone, since ICMS will activate a large population of neurons in the vicinity of the electrode. However, as previously discussed, neighbouring M1 neurons with similar output projections often exhibit synchronous firing. Therefore, many spikes from this synchronous population will be temporally correlated within the coincidence window for synaptic potentiation. The change in motor representation after closed-loop stimulation is consistent with a strengthening of connections from this synchronous assembly to cortical or downstream sites activated by stimulation.

A second example of plastic changes in connectivity resulting from closed-loop stimulation has been recently reported in freely behaving rats (Rebesco et al. 2010), using a measure of functional connectivity based on spontaneous activity. Interestingly, this study also revealed increases in the strength of reciprocal connections from the stimulation site to the trigger cell. A simplistic interpretation of STDP might predict that this connection should be depressed, since the action potential at the recording site precedes synaptic input from the stimulation site. It is possible that motor cortex neurons in vivo do not obey the same STDP rules as have been reported in other preparations. This interpretation would be consistent with the results of Baranyi and Feher (1981), and it has been further noted in slice preparations that STDP rules are influenced by factors including synapse location and dendritic calcium spikes (Froemke et al. 2010). However, it should also be recognised that closed-loop stimulation differs from conventional paired stimulation protocols in that the activity associated with each stimulus do not occur in isolation, but rather as part of a continuous train of pre- and post-synaptic events. The results of stimulation experiments using triplet, quadruplet and naturalistic stimulus trains cannot be explained by a pairwise STDP rule (Sjostrom et al. 2001;

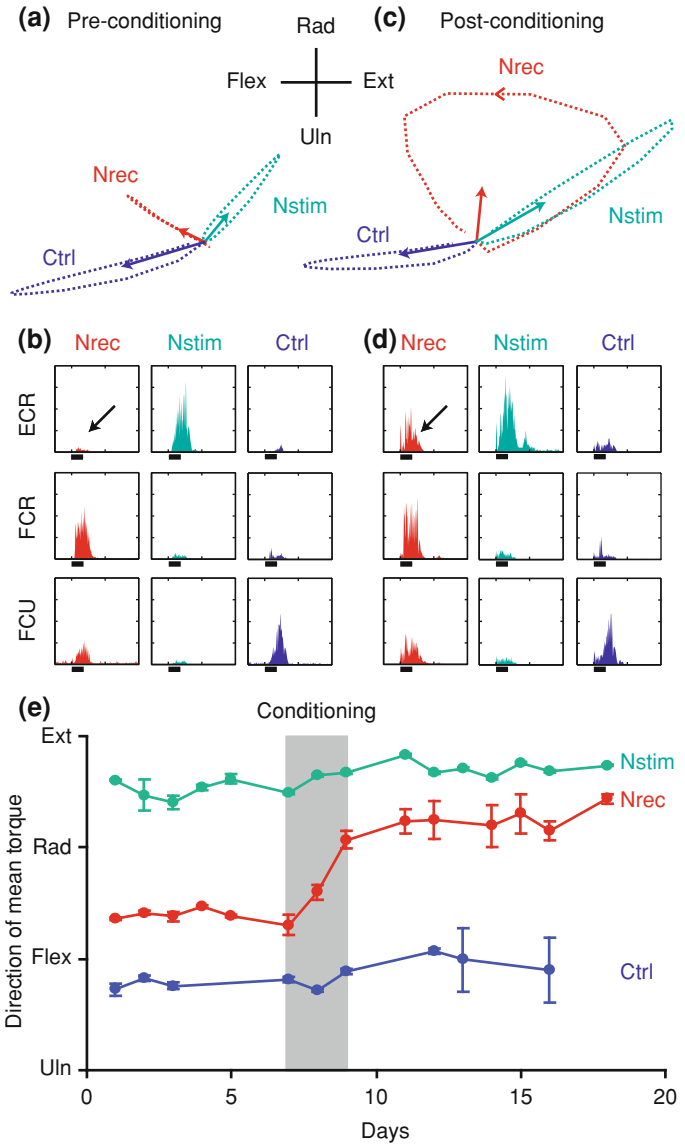

Fig. 1.5 Reorganisation of motor cortex output induced by 2 days continuous closed-loop stimulation of electrode 'Nstim' triggered by a cell recorded on electrode 'Nrec'. **a** Wrist torques generated by ICMS delivered to the cortex. After closed-loop stimulation, the direction of torque elicited from Nrec shifts in the direction of Nstim output. The effect of ICMS at control electrode ('Ctrl') is unchanged. **b** Muscle electromyogram confirms a new output from Nrec electrode to muscle ECR (arrows). **c** Plot of mean direction of torque response shows that in this case changes resulting from closed-loop stimulation (days 7–9) persisted for 9 subsequent days. Reproduced from Jackson et al. (2006a)

Froemke and Dan 2002) and predict potentiation will win out during periods of high pre- and post-synaptic activity irrespective of precise temporal order (Pfister and Gerstner 2006).

1.4.5 Corticospinal Plasticity

As with the cortical map reorganisation seen after skill learning, it is worth remembering that plasticity at the spinal level may contribute to the effects of all three of these cortical stimulation protocols. Iriki et al. (1990) demonstrated that tetanic stimulation of the pyramidal tract enhanced descending EPSPs in spinal interneurons in the cat, so it is likely that cortical stimulation may also affect descending projections. There is also evidence that PAS protocols in humans may also induce changes at the spinal level (Meunier et al. 2007; Lamy et al. 2010). Taylor and Martin (2009) have developed a PAS protocol with interstimulus intervals designed specifically to result in convergence at the motoneurons of descending TMS volleys and afferent stimulation. Using cervicomedullary stimulation to probe the descending pathways, they found evidence for STDP-like changes in the efficacy of corticospinal transmission. There was also an intriguing behavioural effect of this stimulation protocol; subjects made errors in a bimanual force matching task consistent with a discrepancy between perceived and actual force production due to altered corticospinal transmission. Plasticity has now been demonstrated more directly for primate CM connections by closed-loop stimulation of the spinal cord (Fetz et al. 2010). Using action potentials of CM cells to trigger intraspinal stimuli near the terminals of these cells during a day or more of free behaviour led to clear increases in the sizes of post-spike effects obtained in spike-triggered averages of EMG activity. These findings suggest that the same basic Hebbian mechanism of associative plasticity may operate throughout the corticospinal system to shape motor behaviours.

1.5 Conclusions and Future Directions

This chapter has reviewed recent progress in our understanding of how connectivity in the corticospinal system is altered during the acquisition of new motor skills. We have seen how motor cortical maps are dynamic, and that a reorganisation of distributed movement representations is underpinned by changes in the intracortical networks that mediate motor output. Artificial stimulation protocols that impose correlated neuronal activity have revealed Hebbian mechanisms of synaptic potentiation in cortical and spinal connections that bind neurons into functional assemblies. However, there is much that remains to be understood. The corticospinal system is embedded in a larger motor network incorporating recurrent connections with other cortical areas as well as feedback loops through

the basal ganglia and cerebellum, and is influenced by multiple neuromodulatory systems. We are still far from a computational level description of how these different structures contribute to learning and optimising new behaviours. A new skill can be acquired in minutes but may take years of practice to perfect (Crossman 1959). It is possible that the cerebellum is responsible for rapid adaptation driven by movement errors, while motor cortex is involved in the long-term refinement and consolidation of motor skills. Controversy persists over the role of sleep in this process (Song 2009), in particular REM phases during which the motor cortex is highly active (Jackson et al. 2007). Furthermore, the motor system can acquire multiple skills and switch effortlessly between them according to context. If the expansion of cortical territory associated with trained limbs reflects the storage of new skills, it is not clear how this is allocated so as to avoid interference with previous learning (Silva et al. 2009).

Learning is, by its very nature, a non-stationary process, with complex interactions between neural activity, connectivity and behaviour. New techniques for monitoring cell populations over long timescales, coupled with analysis techniques to infer network connectivity will doubtless provide new insights into these problems. But only through the experimental modification of connectivity and behaviour by manipulating activity at the neural level can causal relationships between brain activity, plasticity and learning be established. The ability of non-invasive stimulation methods to enhance learning rates in humans is a step in this direction (Kim et al. 2004; Reis et al. 2009; Galea et al. 2011), but current protocols are limited in their spatial and temporal specificity. Therefore, the use of invasive paired and closed-loop stimulation protocols to modify behaviour in animals (e.g., Rebesco and Miller 2011) will provide a key test for neural theories of learning.

The focus of this chapter has been plasticity during skill learning, but it is increasingly clear that similar mechanisms underlie recovery of function following conditions like stroke or spinal cord injury (Chen et al. 2002). This has led to a surge of interest in stimulation protocols designed to enhance plasticity and promote rehabilitation. At the moment, the emphasis is on non-invasive techniques which, while promising, may ultimately prove to be rather blunt instruments for reshaping connectivity at the neural level. But at the same time, new BMI technologies are being developed that will enable long-term interfacing with the brain at the level of individual neurons. Currently, these technologies are being developed mainly as prostheses to replace lost function, but in future may have application as tools to manipulate plasticity. We are developing techniques to implant multi-electrode stimulating arrays into the spinal cord to elicit functional arm and hand movements after paralysis (Jackson et al. 2006b; Zimmermann et al. 2011) with the aim of using next generation Neurochip implants to implement multi-channel closed-loop stimulation controlled by cortical activity. Such devices could act as artificial pathways from the brain to the motoneurons, bypassing complete transections of the spinal cord. But plasticity arising from closed-loop stimulation suggests an additional application in the case of incomplete injuries to enhance surviving descending pathways and promote rehabilitation. These studies

provide a small glimpse of the future possibilities afforded by BMI technologies to manipulate connectivity through activity-dependent mechanisms. In combination with an understanding of the mechanisms of plasticity and learning, these technologies may allow the formation of new neural circuits to restore function following a wide range of neurological injuries.

References

Adkins DL, Boychuk J, Remple MS, Kleim JA (2006) Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. J Appl Physiol 101:1776–1782

Asanuma H, Arnold A, Zarzecki P (1976) Further study on the excitation of pyramidal tract cells by intracortical microstimulation. Exp Brain Res 26:443–461

Baranyi A, Fehér O (1981) Synaptic facilitation requires paired activation of convergent pathways in the neocortex. Nature 290:413–415

Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232:331–356

Brown TG, Sherrington CS (1912) On the Instability of a Cortical Point. Proc R Soc Lond B 85:250–277

Canolty RT, Ganguly K, Kennerley SW, Cadieu CF, Koepsell K, Wallis JD, Carmena JM (2010) Oscillatory phase coupling coordinates anatomically dispersed functional cell assemblies. Proc Natl Acad Sci U S A 107:17356–17361

Carmena JM, Lebedev MA, Crist RE, O'Doherty JE, Santucci DM, Dimitrov DF, Patil PG, Henriquez CS, Nicolelis MA (2003) Learning to control a brain-machine interface for reaching and grasping by primates. PLoS Biol 1:E42

Carroll TJ, Riek S, Carson RG (2002) The sites of neural adaptation induced by resistance training in humans. J Physiol 544:641–652

Chen R, Cohen LG, Hallett M (2002) Nervous system reorganization following injury. Neuroscience 111:761–773

Cheney PD, Fetz EE (1985) Comparable patterns of muscle facilitation evoked by individual corticomotoneuronal (CM) cells and by single intracortical microstimuli in primates: evidence for functional groups of CM cells. J Neurophysiol 53:786–804

Conner JM, Culberson A, Packowski C, Chiba AA, Tuszynski MH (2003) Lesions of the Basal forebrain cholinergic system impair task acquisition and abolish cortical plasticity associated with motor skill learning. Neuron 38:819–829

Conner JM, Kulczycki M, Tuszynski MH (2010) Unique contributions of distinct cholinergic projections to motor cortical plasticity and learning. Cereb Cortex 20:2739–2748

Crossman ERFW (1959) A theory of the acquisition of speed-skill. Ergonomics 2(153):166

Dum RP, Strick PL (2002) Motor areas in the frontal lobe of the primate. Physiol Behav 77: 677–682

Fetz EE, Cheney PD (1980) Postspike facilitation of forelimb muscle activity by primate corticomotoneuronal cells. J Neurophysiol 44:751–772

Fetz EE, Nishimura Y, Eaton RW, Perlmutter SI (2010) Primate corticospinal connections can be strengthened by prolonged spike-triggered stimulation of spinal cord during free behavior. Soc Neurosci Abstr 899.2

Froemke RC, Dan Y (2002) Spike-timing-dependent synaptic modification induced by natural spike trains. Nature 416:433–438

Froemke RC, Letzkus JJ, Kampa BM, Hang GB, Stuart GJ (2010) Dendritic synapse location and neocortical spike-timing-dependent plasticity. Front Synaptic Neurosci 2:29

Galea JM, Vazquez A, Pasricha N, Orban de Xivry JJ, Celnik P (2011) Dissociating the roles of the cerebellum and motor cortex during adaptive learning: the motor cortex retains what the cerebellum learns. Cereb Cortex 21:1761–1770

Ganguly K, Carmena JM (2009) Emergence of a stable cortical map for neuroprosthetic control. PLoS Biol 7:e1000153

Ganguly K, Dimitrov DF, Wallis JD, Carmena JM (2011) Reversible large-scale modification of cortical networks during neuroprosthetic control. Nat Neurosci 14:662–667

Ghosh S, Porter R (1988) Corticocortical synaptic influences on morphologically identified pyramidal neurones in the motor cortex of the monkey. J Physiol 400:617–629

Hadipour-Niktarash A, Lee CK, Desmond JE, Shadmehr R (2007) Impairment of retention but not acquisition of a visuomotor skill through time-dependent disruption of primary motor cortex. J Neurosci 27:13413–13419

Hebb DO (1949) The Organization of Behavior: a Neuropsychological Theory. Wiley, New York

Heffner R, Masterton B (1975) Variation in form of the pyramidal tract and its relationship to digital dexterity. Brain Behav Evol 12:161–200

Histed MH, Bonin V, Reid RC (2009) Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. Neuron 63:508–522

Huntley GW, Jones EG (1991) Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: a correlative anatomic and physiological study. J Neurophysiol 66:390–413

Iriki A, Keller A, Pavlides C, Asanuma H (1990) Long-lasting facilitation of pyramidal tract input to spinal interneurons. NeuroReport 1:157–160

Jackson A, Fetz E (2011) Interfacing With the Computational Brain. IEEE Trans Neural Sys Rehabil Eng. doi:10.1109/TNSRE.2011.2158586

Jackson A, Spinks RL, Freeman TC, Wolpert DM, Lemon RN (2002) Rhythm generation in monkey motor cortex explored using pyramidal tract stimulation. J Physiol 541:685–699

Jackson A, Gee VJ, Baker SN, Lemon RN (2003) Synchrony between neurons with similar muscle fields in monkey motor cortex. Neuron 38:115–125

Jackson A, Mavoori J, Fetz EE (2006a) Long-term motor cortex plasticity induced by an electronic neural implant. Nature 444:56–60

Jackson A, Moritz CT, Mavoori J, Lucas TH, Fetz EE (2006b) The neurochip BCI: towards a neural prosthesis for upper limb function. IEEE Trans Neural Sys Rehabil Eng 14:187–190

Jackson A, Mavoori J, Fetz EE (2007) Correlations between the same motor cortex cells and arm muscles during a trained task, free behavior, and natural sleep in the macaque monkey. J Neurophysiol 97:360–374

Jankowska E, Padel Y, Tanaka R (1975) The mode of activation of pyramidal tract cells by intracortical stimuli. J Physiol 249:617–636

Kilavik BE, Roux S, Ponce-Alvarez A, Confais J, Grün S, Riehle A (2009) Long-term modifications in motor cortical dynamics induced by intensive practice. J Neurosci 29: 12653–12663

Kim YH, Park JW, Ko MH, Jang SH, Lee PK (2004) Facilitative effect of high frequency subthreshold repetitive transcranial magnetic stimulation on complex sequential motor learning in humans. Neurosci Lett 367:181–185

Kleim JA, Lussnig E, Schwarz ER, Comery TA, Greenough WT (1996) Synaptogenesis and Fos expression in the motor cortex of the adult rat after motor skill learning. J Neurosci 16: 4529–4535

Kleim JA, Barbay S, Nudo RJ (1998) Functional reorganization of the rat motor cortex following motor skill learning. J Neurophysiol 80:3321–3325

Kleim JA, Hogg TM, VandenBerg PM, Cooper NR, Bruneau R, Remple M (2004) Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. J Neurosci 24:628–633

Komiyama T, Sato TR, O'Connor DH, Zhang YX, Huber D, Hooks BM, Gabitto M, Svoboda K (2010) Learning-related fine-scale specificity imaged in motor cortex circuits of behaving mice. Nature 464:1182–1186

Kuypers HGJM (1981) Anatomy of the descending pathways. In: Brookhart JM, Mountcastle VB (eds) Handbook of physiology sect 1 vol 2 part 1. Williams and Wilkins, Baltimore

Lamy JC, Russmann H, Shamim EA, Meunier S, Hallett M (2010) Paired associative stimulation induces change in presynaptic inhibition of Ia terminals in wrist flexors in humans. J Neurophysiol 104:755–764

Lashley KS (1950) In search of the engram. Soc Exp Biol 4:454–482

Lawrence DG, Kuypers HG (1968) The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. Brain 91:1–14

Lawrence DG, Porter R, Redman SJ (1985) Corticomotoneuronal synapses in the monkey: light microscopic localization upon motoneurons of intrinsic muscles of the hand. J Comp Neurol 232:499–510

Markram H, Lübke J, Frotscher M, Sakmann B (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 275:213–215

Martin JH, Kably B, Hacking A (1999) Activity-dependent development of cortical axon terminations in the spinal cord and brain stem. Exp Brain Res 125:184–199

Mavoori J, Jackson A, Diorio C, Fetz E (2005) An autonomous implantable computer for neural recording and stimulation in unrestrained primates. J Neurosci Methods 148:71–77

McKiernan BJ, Marcario JK, Karrer JH, Cheney PD (1998) Corticomotoneuronal postspike effects in shoulder, elbow, wrist, digit, and intrinsic hand muscles during a reach and prehension task. J Neurophysiol 80:1961–1980

Meunier S, Russmann H, Simonetta-Moreau M, Hallett M (2007) Changes in spinal excitability after PAS. J Neurophysiol 97:3131–3135

Meyer-Lohmann J, Christakos CN, Wolf H (1986) Dominance of the short-latency component in perturbation induced electromyographic responses of long-trained monkeys. Exp Brain Res 64:393–399

Monfils MH, Teskey GC (2004) Skilled-learning-induced potentiation in rat sensorimotor cortex: a transient form of behavioural long-term potentiation. Neuroscience 125:329–336

Monfils MH, VandenBerg PM, Kleim JA, Teskey GC (2004) Long-term potentiation induces expanded movement representations and dendritic hypertrophy in layer V of rat sensorimotor neocortex. Cereb Cortex 14:586–593

Nimchinsky EA, Sabatini BL, Svoboda K (2002) Structure and function of dendritic spines. Annu Rev Physiol 64:313–353

Nudo RJ, Jenkins WM, Merzenich MM (1990) Repetitive microstimulation alters the cortical representation of movements in adult rats. Somatosens Mot Res 7:463–483

Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM (1996) Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. J Neurosci 16:785–807

Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M (1995) Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. J Neurophysiol 74:1037–1045

Penfield W, Jasper HH (1954) Epilepsy and the functional anatomy of the human brain. Little Brown, Boston

Pérez-Otaño I, Ehlers MD (2005) Homeostatic plasticity and NMDA receptor trafficking. Trends Neurosci 28:229–238

Pfister JP, Gerstner W (2006) Triplets of spikes in a model of spike timing-dependent plasticity. J Neurosci 26:9673–9682

Phillips CG, Zeki S, Barlow HB (1984) Localization of function in the cerebral cortex. Past, present and future. Brain 107:327–361

Plautz EJ, Milliken GW, Nudo RJ (2000) Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. Neurobiol Learn Mem 74:27–55

Rathelot JA, Strick PL (2006) Muscle representation in the macaque motor cortex: an anatomical perspective. Proc Natl Acad Sci U S A 103:8257–8262

Rathelot JA, Strick PL (2009) Subdivisions of primary motor cortex based on cortico-motoneuronal cells. Proc Natl Acad Sci U S A 106:918–923

Rebesco JM, Miller LE (2011) Enhanced detection threshold for in vivo cortical stimulation produced by Hebbian conditioning. J Neural Eng 8:016011

Rebesco JM, Stevenson IH, Körding KP, Solla SA, Miller LE (2010) Rewiring neural interactions by micro-stimulation. Front Sys Neurosci 4:39

Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, Celnik PA, Krakauer JW (2009) Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A 106:1590–1595

Remple MS, Bruneau RM, VandenBerg PM, Goertzen C, Kleim JA (2001) Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization. Behav Brain Res 123:133–141

Rioult-Pedotti MS, Friedman D, Hess G, Donoghue JP (1998) Strengthening of horizontal cortical connections following skill learning. Nat Neurosci 1:230–234

Rioult-Pedotti MS, Friedman D, Donoghue JP (2000) Learning-induced LTP in neocortex. Science 290:533–536

Rioult-Pedotti MS, Donoghue JP, Dunaevsky A (2007) Plasticity of the synaptic modification range. J Neurophysiol 98:3688–3695

Sakamoto T, Porter LL, Asanuma H (1987) Long-lasting potentiation of synaptic potentials in the motor cortex produced by stimulation of the sensory cortex in the cat: a basis of motor learning. Brain Res 413:360–364

Schieber MH (2001) Constraints on somatotopic organization in the primary motor cortex. J Neurophysiol 86:2125–2143

Schieber MH (2002) Training and synchrony in the motor system. J Neurosci 22:5277–5281

Schneider C, Capaday C (2003) Progressive adaptation of the soleus H-reflex with daily training at walking backward. J Neurophysiol 89:648–656

Shen K, Cowan CW (2010) Guidance molecules in synapse formation and plasticity. Cold Spring Harb Perspect Biol 2(4):a001842

Shinoda Y, Yokota J, Futami T (1981) Divergent projection of individual corticospinal axons to motoneurons of multiple muscles in the monkey. Neurosci Lett 23:7–12

Silva AJ, Zhou Y, Rogerson T, Shobe J, Balaji J (2009) Molecular and cellular approaches to memory allocation in neural circuits. Science 326:391–395

Sjöström PJ, Turrigiano GG, Nelson SB (2001) Rate, timing, and cooperativity jointly determine cortical synaptic plasticity. Neuron 32:1149–1164

Song S (2009) Consciousness and the consolidation of motor learning. Behav Brain Res 196: 180–186

Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J (2000) Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 123:572–584

Taylor JL, Martin PG (2009) Voluntary motor output is altered by spike-timing-dependent changes in the human corticospinal pathway. J Neurosci 29:11708–11716

Taylor DM, Tillery SI, Schwartz AB (2002) Direct cortical control of 3D neuroprosthetic devices. Science 296:1829–1832

Wolpaw JR, Kieffer VA, Seegal RF, Braitman DJ, Sanders MG (1983) Adaptive plasticity in the spinal stretch reflex. Brain Res 267:196–200

Woolsey CN, Settlage PN, Meyer DR, Sencer W, Hamuy TP, Travis AM (1952) Patterns of localization in precentral and 'supplementary' motor areas and their relation to the concept of a premotor region. Res Publ Ass Nerv Ment Dis 30:238–264

Xu T, Yu X, Perlik AJ, Tobin WF, Zweig JA, Tennant K, Jones T, Zuo Y (2009) Rapid formation and selective stabilization of synapses for enduring motor memories. Nature 462:915–919

Zimmermann JB, Seki K, Jackson A (2011) Reanimating the arm and hand with intraspinal microstimulation. J Neural Eng 8:054001

Chapter 2
Interactions Between Premotor and Motor Cortices in Non-Human Primates

R. N. Lemon

Abstract This review is concerned with a detailed examination of the neurophysiological mechanisms that allow fast interactions between two key components of the 'visuomotor grasping network' in the primate brain: ventral premotor cortex (PMv) and primary motor cortex (M1). It first reviews the anatomical linkages between them and then surveys a number of studies which have together shown that PMv can modulate activity of grasp-related activity in M1 in a grasp-specific fashion, and in particular can either facilitate or suppress M1 outputs controlling intrinsic hand muscles. The mechanisms subserving the interactions between PMv and M1, which are reciprocal, could allow for fast selection of M1 outputs that would be appropriate for the grasp of visible objects.

2.1 Introduction

In 1995 an important review paper by Marc Jeannerod[1] et al. (1995) first suggested the concept of a 'visuomotor grasping circuit'. Grasp of objects is of course fundamental to our daily interaction with the environment, and the visual guidance

[1] Marc Jeannerod RIP 2011.

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of skilled prehension and manipulation of objects is characteristic of the human motor system and its engagement in creative activities such as art, sculpture and music making as well as in technological development, tool use and manufacture. The highly-cited review by Jeannerod and his colleagues (549 citations in mid-2011) opened up a new approach to the study of cortical processing, no longer based on the properties of particular cortical areas, but focused on the transmission of information between areas: They suggested that "the transformation of an object's intrinsic properties into specific grips takes place in a circuit that is formed by the inferior parietal lobule and the inferior premotor area (area F5). Neurons in both these areas code size, shape and orientation of objects, and specific types of grip that are necessary to grasp them."

Interestingly research in the years since has especially highlighted the position of area F5, the rostral subdivision of the ventral premotor cortex (PMv), as a node within this circuit. Work led particularly by Giacomo Rizzolatti and the Parma group revealed why this area should be the focus of so much interest (Rizzolatti and Luppino 2001; Davare et al. 2011). First, the existence of visuomotor "canonical neurons" that discharge during selection, preparation and execution of the particular types of grasping action, and which appear to be activated by visual information about graspable objects represented in the posterior parietal cortex (area AIP). Second, the presence of connections with prefrontal cortex, which opened up possible pathways transmitting information about how the grasp should reflect the manner in which the object was to be used (the object's 'affordance'). Third, the existence of mirror neurons, activated not only during self-executed grasp but also during action observation of grasp. Finally, the demonstration that reversible inactivation of area F5 induces a deficit whereby the monkey shows no obvious paresis but can no longer preshape the hand appropriately for grasp of a particular object.

Pandya and Kuypers (1969) had first analysed the likely routes through which visual information could be accessed by the motor cortex. They showed that primary motor cortex (M1) did not receive any inputs from the visual associative areas in the posterior parietal cortex, but that these inputs terminated further forward in a number of premotor areas, including the ventral (PMv) and dorsal (PMd) premotor areas and the SMA. This early paper suggested that projections from these areas back into M1 might then allow vision to guide the selection and execution of fine hand movements. This was confirmed by elegant lesions studies (Haaxma and Kuypers 1974; Halsband and Passingham 1982).

Although there is evidenced that all of the major premotor areas interact with M1 during preparation and execution of movement, this review will very much focus on the interactions between PMv and M1 in the non-human primate, as a model of these wider network activities. Again, although we will focus mainly on cortico-cortical interactions, this is not to forget the importance of subcortical (pallidal and particularly cerebellar) interactions. For example, both AIP and PMv are the source of inputs to the pontine nuclei (Glickstein et al. 1985) and the cortico-cerebellar loop is also critical to visuomotor control (Stein and Glickstein 1992).

2.2 How Does PMv Influence the Motor Apparatus of the Hand? Descending Projections to the Brainstem and Spinal Cord

Whilst PMv has a low-threshold motor representation of the hand and digits (e.g. Godschalk et al. 1995), it does not give rise to many corticospinal projections (only 4 % of the total frontal lobe corticospinal projection (Dum and Strick 1991) and these terminate mostly in the upper cervical segments of the spinal cord (He et al. 1993). This established view has recently been re-examined by Borra et al. (2010) which investigated in detail both brainstem and spinal targets of specific regions of PMv.

Borra et al. (2010) confirmed by double injection that the subdivision of F5 (area F5p) that projects to the hand area of M1 (see Sect. 2.3 below), also projects to cervical spinal cord. The cytoarchitectonic division F5p (posterior) is located in the dorsal and posterior part of the inferior bank of the arcuate sulcus (Belmalij et al. 2009). Injection of anterograde tracers in this subdivision revealed descending projections to brainstem structures that are themselves origins of descending pathways to the spinal cord (including the superior colliculus, reticular formation and peri-aqueductal grey), and to structures involved in cerebellar motor circuits, including the red nucleus and pontine nuclei. Although Borra et al. (2010) found some sparse projections from area F5p to the lower cervical cord (segments C6-T1, which contain the motor nuclei controlling the muscles acting on the hand and digits; Jenny and Inukai 1983), the corticospinal projections seem to be mainly focused on the upper cervical segments (cf. He et al. 1993). There were no projections beyond T6. It is puzzling that despite the very high incidence of neurons in F5 with activity related to the ipsilateral hand, there are few projections to the ipsilateral grey matter.

It has been hypothesised that the F5 output maybe particularly concerned with projections to the C3-C4 propriospinal system, which originate from the spinal intermediate zone in these segments. This system was originally proposed to support accurate reaching in the cat, but is thought to be more important for grasping in the primate (Isa et al. 2007). It is also thought to mediate the recovery of grasp after spinal lesions at the mid-cervical (C5) level which interrupt the corticospinal input to the lower cervical segments, including the direct cortico-motoneuronal (CM) component. Importantly, such lesions result in an immediate and severe impairment of precision grip (Sasaki et al. 2004); the process of recovery may well involve a number of different brainstem and propriospinal mechanisms (Zaaimi et al. 2012; Alstermark et al. 2011).

Despite the interesting possibilities raised by the distinctive pattern of F5 corticospinal projections, the overall conclusion must be that (a) this represents a comparatively minor component of the total frontal lobe corticospinal output and that (b) connections to the lower cervical cord are relatively weak, and do not include CM projections (Lemon 2008). Although Borra et al. (2010) concluded that the "F5 hand field can control hand muscle motoneurons through C3-C4

propriospinal neurons", it is clear that with stimulation of F5 with single pulses and intensities that do not result in concomitant activation of M1 (see Sect. 2.5.3 below), responses in hand muscle motoneurons are rarely observed (Shimazu et al. 2004; Prabhu et al. 2009). When multiple pulses and higher intensities are used to evoke motor responses from F5, these responses are lost when M1 is acutely and reversibly inactivated (Shimazu et al. 2004; Schmidlin et al. 2008). Importantly Schmidlin et al. (2008) showed that this effect was not due to any loss of tonic facilitatory output from M1 that might be needed to reveal a F5-C3-C4 propriospinal linkage (see their Fig. 2.6).

Recent physiological studies comparing antidromic activation of pyramidal tract neurons (PTNs) in F5 and M1 (Kraskov et al. 2009; Vigneswaran et al. 2011) have shown that F5 does not contain many PTNs with very short antidromic latencies that are commonly found in M1, and which presumably have fast-conducting axons and large somata (Sakai and Woody 1988). So the F5 corticospinal output (like that of other secondary motor areas; Maier et al. 2002) is rather different to that from M1.

2.3 How Does PMv Influence the Motor Apparatus of the Hand? Anatomy of PMv-M1 Connections

The cortico-cortical network highlighted by Jeannerod et al. (1995) represents an important route through which PMv can access the many corticofugal outputs from M1 to the brainstem and spinal cord that are concerned with hand control. These include the CM component of the corticospinal output, but it is important to stress that this system operates in parallel with other descending systems that target hand motoneurons indirectly (see Lemon 2008).

Gerbella et al. (2011) have recently discussed the different pattern of cortico-cortical connections established by the three sub-divisions of area F5. Of these, the subdivision of most relevance to this review is the posterior region (area F5p), which is a hand-related field in which 'canonical' visuomotor neurons responsive to observation and grasp of 3D objects are particularly prominent (Raos et al. 2006; Umilta et al. 2007) F5p has strong reciprocal connections to AIP in the posterior parietal cortex (Pandya and Kuypers 1969; Gharbawie et al. 2011). Sub-division F5p also provides the main connections with the M1 hand area (Muakkassa and Strick 1979; Godschalk et al. 1984), which are also reciprocal. Unlike the more anterior region of F5 (F5a), it has only weak connections to prefrontal areas. In terms of functional analysis, it is important to stress that all three subdivisions (including F5c in which mirror neurons are primarily located) are densely interconnected (Gerbella et al. 2011).

The PMv is also strongly interconnected with homotopical areas in the contralateral hemisphere (Dancause et al. 2007; Boussaoud et al. 2005; Rouiller et al. 1994), which contrasts with the sparser callosal interconnections found for the M1 hand area (Rouiller et al. 1994).

2.4 Neurophysiology of Premotor-Motor Connections

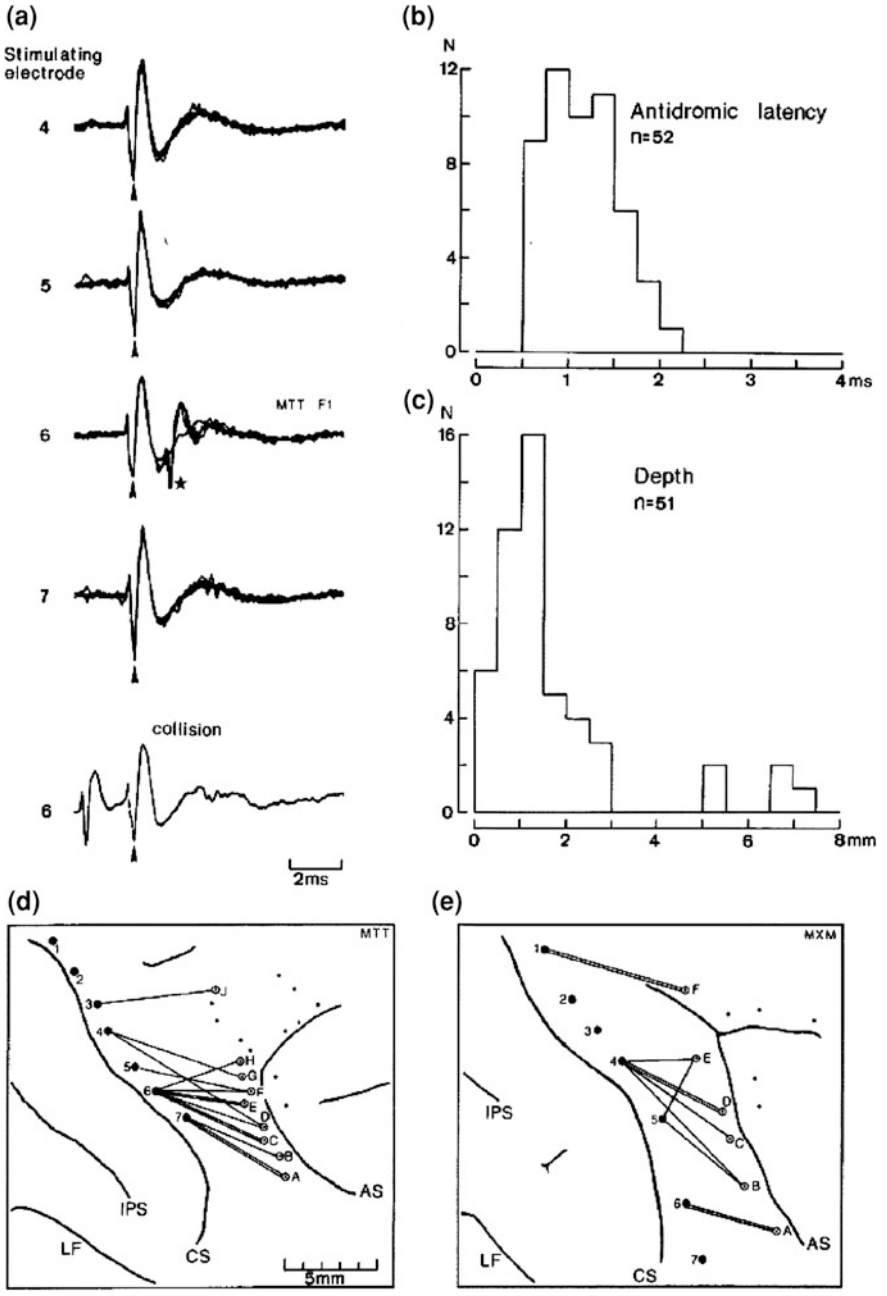
2.4.1 Antidromic Responses in Cortico-Cortical Neurons

The early anatomical descriptions of the PMv-M1 projections encouraged Godschalk et al. (1984) to investigate their physiological characteristics. In anaesthetised macaque monkeys they placed a row of seven stimulating electrodes positioned a few mm rostral to the central sulcus and spanning the arm/hand/face representations in M1 (Fig. 2.1d, e). They then recorded from the PMv ('post-arcuate region') searching for neurons with latency-invariant antidromic responses (Fig. 2.1a). These cortico-cortical neurons were found mostly at rather superficial locations (0.3–1.5 mm deep to the cortical surface; Fig. 2.1c) suggesting that they were in layers II or III (which are one important source of cortico-cortical projections; Jones and Wise 1977; Douglas and Martin 2004), rather than in lamina V. Each M1 stimulation site was separated by around 2 mm; even with a maximum stimulation intensity of 500 μA, most of the PMv neurons could be activated only from a single site, which suggests a rather specific set of projections. These projections generally ran in a postero-medial direction (Fig. 2.1d, e). Antidromic latencies ranged from 0.6 to 2.1 ms (mean 1.2 ms; Fig. 2.1b); since the distances between sites in PMv yielding antidromic responses to stimulation sites in M1 were around 8–10 mm, this would put an upper limit on the conduction velocity of cortico-cortical axons of around 17 m/s, with most <10 m/s.

2.4.2 Signs of Synaptic Interactions Between PMv and M1 at the Single Neuron Level

Many years after the publication of Godschalk et al. (1984), we developed a means of simultaneous recording of multiple neurons from both PMv and M1 hand regions in the awake, behaving monkey (Umilta et al. 2007). This approach was used to allow us examine the time course of activity in these two interconnected areas during performance of visually-guided reach-to-grasp task, in which monkeys were first shown a pseudo-randomly ordered set of graspable objects (examples in Fig. 2.2a), and then cued to grasp and displace them by a controlled amount. This study showed that both F5 and M1 neurons showed patterns of activity that were specific to the grasp needed for a particular object. However at the population level, the onset of this grasp-specific activity was clearly earlier in F5 than in M1, in keeping with the original hypothesis advanced by Jeannerod et al. (1995). The result is probably explained by the projection from regions of the posterior parietal cortex (and especially area AIP) to F5 (but not to M1) of information related to the visual properties of graspable objects.

An obvious question is whether the visuomotor neurons that are activated at short-latency by the presence of graspable objects can be shown to be connected to



M1 neurons involved in the grasping action. We have used cross-correlation methods (see Baker et al. 2001) to examine this possibility, but analysis of many pairs of simultaneously recorded F5 and M1 neurons did not yield any signs of

◀ **Fig. 2.1** Identifying cortico-cortical projections from PMv to M1. Topographic distribution of projections from PMv to M1, as identified by antidromic identification of cortico-cortical neurons in PMv responding to electrical stimulation of the M1 hand area. **a** Recording from single PMv neuron (located in penetration F in **d**) activated antidromically by single-pulse intracortical stimulation within M1 (electrode 6). Antidromic spike indicated by *asterisk*. Four sweeps at a current strength (150 μA) threshold for this response have been superimposed, together with one sweep at sub-threshold (no antidromic spike). The antidromic nature of the response is confirmed by collision with a spontaneous spike (*bottom trace* in **a**). Stimulation at adjacent sites (4, 5 and 7) did not activate the neuron. **b** Distribution of antidromic latencies of PMv neurons responding to M1 stimulation. Most responded within 0.5–2.0 ms. **c** Depth distribution of antidromically activated PMv neurons; most were recorded superficially (<1.5 mm from cortical surface). **d**, **e** Location of penetrations made in periarcuate cortex in two monkeys. Those that contained neurons antidromically activated from M1 are indicated by Θ and joined by a *solid line* to the site in M1 from which the response was obtained. *Dots* indicate penetrations in which no antidromic responses were obtained. Note consistent direction of projections. No neuron was antidromically activated from more than one M1 site. *CS* central sulcus, *AS* arcuate sulcus, *IPS* intraparietal sulcus, *LF* lateral fissure (Gosdchalk et al. 1984, Fig. 2.4, with permission)

correlation peaks indicative of synaptic connectivity (T. Brochier, personal communication). There are two possible reasons for this negative result: first, it is likely that both samples were heavily biased towards large pyramidal neurons in lamina V, whereas many of the neurons giving rise to cortico-cortical projections are in the upper laminae (see above), and second, there is accumulating evidence that the premotor-motor cortex connections are relatively indirect (see below), and may be too weak to show positive features in cross-correlograms of spike trains.

2.4.3 Responses of Single M1 Neurons to Stimulation of Area F5

An alternative approach was to stimulate in one area, while recording from single neurons in the other; by activating many cortico-cortical projections, some of which might converge at the single neuron level, it was anticipated that signs of F5-M1 synaptic connections might be easier to detect. Therefore, we adapted the technique used by Umilta et al. (2007) to allow us to look for responses in M1 to single-pulse intracortical stimulation within the F5 subdivision of the PMv, and vice versa (Kraskov et al. 2011). In this study all the sites (recording and stimulation) were first characterised as having neurons with clear grasp-related activity (Fig. 2.2a, b); their locations are shown in Fig. 2.2c, d. These recordings were biased towards location in deeper laminae and used much weaker stimuli (maximum 40 μA), so it was unsurprising that we did not encounter any antidromic responses. On the other hand, synaptic responses were quite common: for M1 neurons, around 34 % showed responses to F5 stimulation, with an identical proportion of F5 neurons (34 %) responding to M1 stimuli.

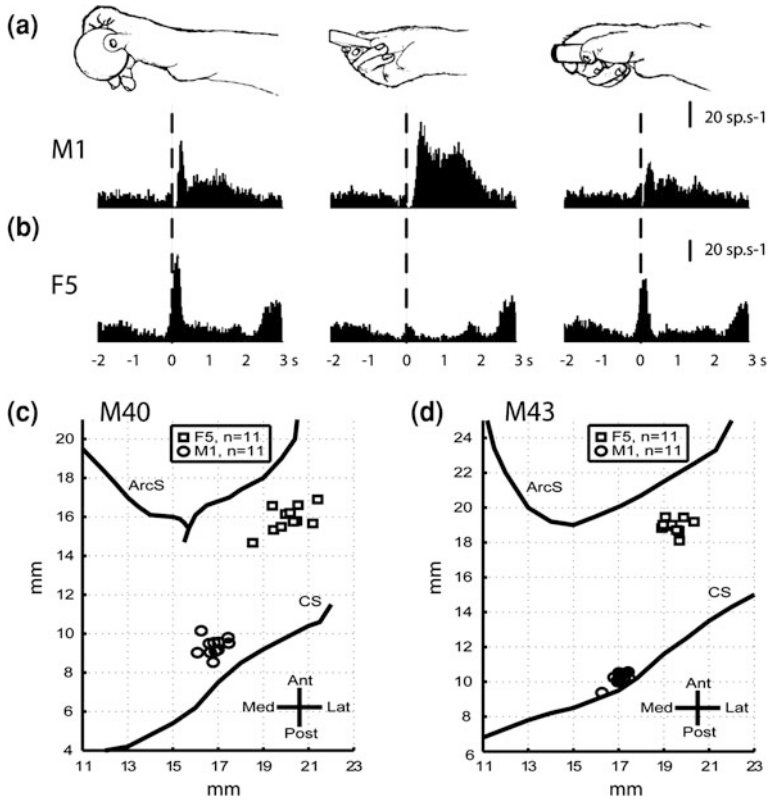


Fig. 2.2 Grasp-related activity and location of paired stimulation and recording sites in M1 and F5. **a** Hand postures used for grasping of three different objects. **b** Typical grasp-related activity of a single neuron recorded in M1 (*top*) and another in F5 (*bottom*) hand areas. Histograms of spike activity are referenced to the moment at which the monkey released a homepad to reach out, grasp and displace the object (time zero, *vertical dashed line*). **c**, **d** Chamber maps from two monkeys (M42, M43) based on MRI and direct stereotactic measurements of the arcuate (ArcS) and central (CS) sulci at surgery. Symbols mark surface location of pairs of electrode penetrations made in area F5 (*squares*) and M1 (*circles*) in the two monkeys

The responses observed were dominated by excitatory effects (Fig. 2.3). Pure excitatory peaks (Fig. 2.3a, b) were most commonly observed (53 % of responses). These occurred at short-latency (1.8–3.0 ms) and were of brief duration ($\sim$1 ms). Purely inhibitory responses (Fig. 2.3e, f) had slightly longer latencies (2–5 ms) and were of small amplitude and longer duration (5–7 ms). They accounted for only 13 % of responses, whereas mixed excitation then inhibition (Fig. 2.3c, d) was seen in 34 % of responses. Many excitatory responses exhibited double peak responses, with a second excitatory peak following the first by around 6 ms (see Kraskov et al. 2011). These authors also examined the effect of stimulus intensity, by comparing responses in neurons at a low (20 μA) and at a higher

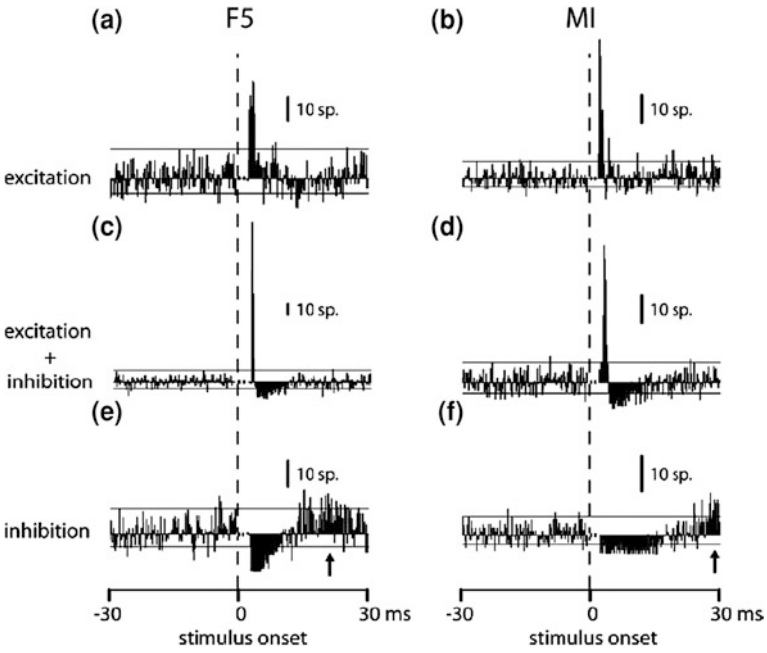


Fig. 2.3 Types of synaptic response in F5 neurons to stimulation of M1 hand area. On the left are shown responses of single F5 neurons to single-pulse ICMS (40 μA). Peristimulus time histograms (PSTH) are synchronised to stimulus delivery (*dashed vertical line* at time zero). The data shown are after correction for any changes in the average instantaneous firing rate over the course of the pre-stimulus period. Confidence limits shown are +2 and –1 SD above and below this value, respectively. The break in the PSTH just after zero reflects the dead-time of the discriminator (time for discriminator to be able to accurately detect spikes after recovery from large stimulus artefact). **a**, **b** Pure excitatory responses, which had short-latency and were very brief (**a**, $n = 2138$ stimuli; **b**, $n = 1939$). **c**, **d** Combined early excitatory plus later and longer lasting inhibitory responses (**c** $n = 4158$; **d** $n = 1881$). **e**, **f** Pure inhibitory responses: note the rebound in activity at the end of the inhibitory period (*arrows*) (**e**, $n = 3355$; **d**, $n = 4246$). Note that similar types of response were obtained in M1 neurons to stimulation of F5 (right hand column). From Kraskov et al. 2011 (with permission)

intensity (40 μA). They found that inhibitory effects were more pronounced with the stronger shocks.

Careful examination of the responses suggested the following: First, although the excitatory responses were of short-latency (Fig. 2.3a), they showed significant latency jitter to successive shocks, indicating that they were mediated by an oligosynaptic, rather than a monosynaptic pathway (see Fig. 2.5e). One possibility is that intracortical stimuli within F5, for example, activate the axons of cortico-cortical neurons which converge and terminate in a rather specific manner in M1 on local excitatory interneurons, which in turn synapse on pyramidal neurons. This is based on the fact that responses were found for only about a third of the paired sites tested, and that a given neuron showed rather different effects (e.g. single or double excitatory peak, or inhibition or no response) when tested from different sites.

Second, M1 pyramidal cells can also be inhibited by cortico-cortical inputs, through the action of local excitatory inputs to inhibitory interneurons (Fig. 2.3e). It is speculated that the convergence of these inhibitory inputs is greater than for excitatory inputs on pyramidal neurons, as this might explain the predominant inhibition at higher stimulus strengths. Interestingly, an earlier report by Tokuno and Nambu (2000), who used relatively strong stimuli (100–150 μA), found that responses of PTNs in M1 to PMv stimulation were dominated by long-lasting (90 ms) inhibition; 23 of 27 PTNs showed pure inhibitory responses, 11 showed excitation–inhibition, and none showed pure excitation. This is clearly a very different set of results to the predominantly facilitatory effects reported by Kraskov et al. (2011). Similarly, the strong currents induced by TMS in humans might explain why in general inhibitory effects have dominated reports using TMS [but see Davare et al. (2008) for an important exception].

2.5 Effects of Stimulating PMv on Corticospinal Outputs from M1

2.5.1 EMG Responses to Cortical Stimulation in Sedated Monkeys

A complementary approach was introduced to demonstrate that PMv-M1 interactions directly influence the corticospinal output from M1 (Cerri et al. 2003). Here the idea was to use a single intracortical stimulus to generate descending activity from M1 that discharged motoneurons supplying the hand muscles, as detected by a short-latency EMG response (similar to the MEP in human TMS studies). One could then examine the effects on the EMG response of conditioning stimuli delivered to PMv. Cerri et al. (2003) found that single or double stimuli delivered to F5, which given alone produced no EMG response, could produce robust facilitation of EMG responses evoked from the M1 hand area (Fig. 2.4). The monkeys used in this study were chronically implanted with small arrays of intracortical microwires, located in F5 and M1 regions that yielded digit movements in response to repetitive intracortical stimulation (rICMS); the most effective F5 electrodes were located in the region we now recognise as F5p.

The significance of these findings was the demonstration of a fast and effective route through which F5 could modulate the M1 output controlling hand muscles, which is of obvious potential importance for visuomotor coordination.

Condition-test experiments were carried out using pairs of intracortical microwires, one as cathode and the other as anode. Separate controls established that the direct effects of the stimuli used did not spread much more than 1–2 mm from the stimulation site i.e. there was no direct spread of current from F5 to M1. The studies were carried out with monkeys lightly sedated with ketamine/medetomidine HCl, such that there was still some background tone in the hand muscles.

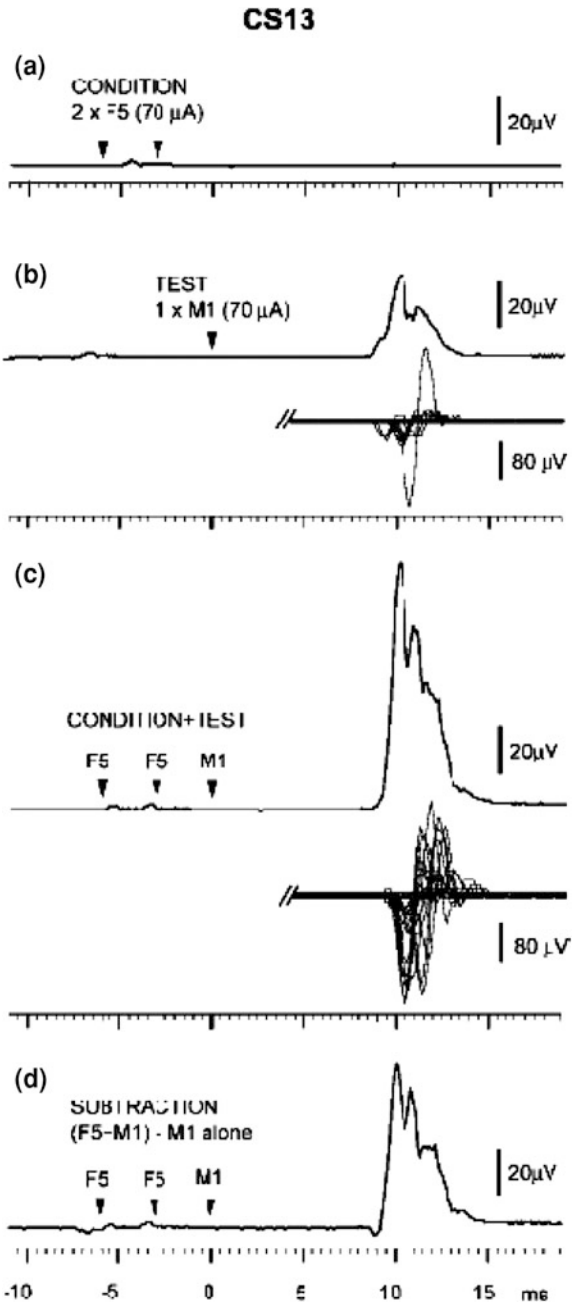


Fig. 2.4 Facilitation of responses evoked from M1 by conditioning stimulation of area F5. Typical set of results from a monkey under light ketamine sedation. Averages of rectified electromyographic (EMG; 50 sweeps) recorded from thenar muscles contralateral to stimulated cortex. **a** Double F5 conditioning shocks (2×70 μA, 3 ms separation) did not evoke an EMG response. **b** Single test shocks applied to M1 (1×70 μA) yielded a clear short-latency EMG effect with an onset latency of about 8 ms; 23 superimposed sweeps are shown below the average at the same time scale to indicate variation in amplitude and latency of the test responses. **c** double F5 conditioning shocks delivered before the M1 test shock (condition-test interval: 3 ms) greatly facilitated the response; 23 superimposed unrectified sweeps are shown below the average at the same time scale to indicate variation in amplitude and latency of the conditioned responses. **d** Subtraction (average in **c** minus average in **b**) shows the additional effect of the conditioning shocks. (from Cerri et al. 2003, with permission)

Under these conditions, the facilitation of the EMG responses from F5 was large (Fig. 2.4d): around 4-fold with single F5 pulses, and up to 12-fold with double pulses, given 3 ms apart. These values are considerably larger than obtained

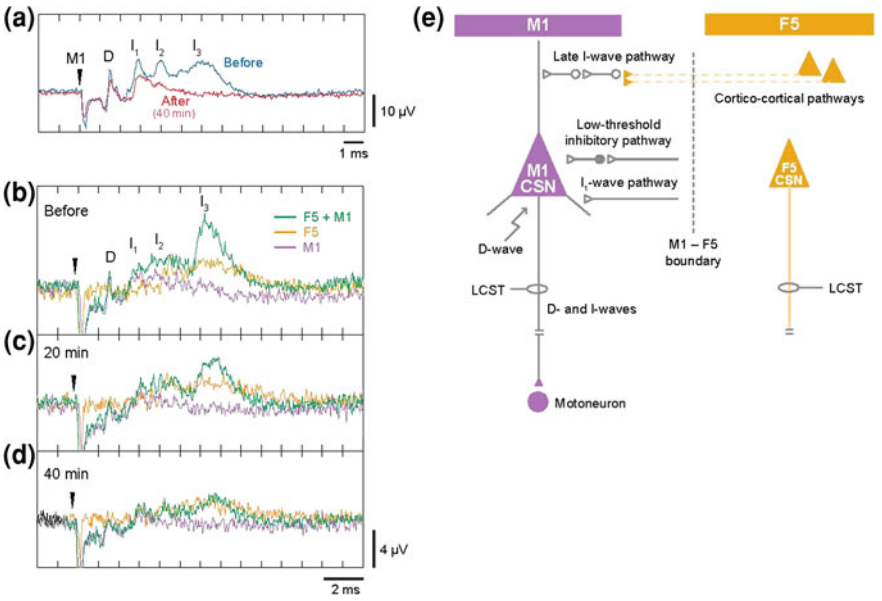


Fig. 2.5 Facilitation of corticospinal outputs from M1 by ventral premotor cortex (F5) stimulation. **a** Intracortical stimulation with a single pulse in the hand area of M1 evokes a series of descending corticospinal volleys: the D (direct) wave and a number of indirect (I) waves (*blue trace*). Forty minutes after microinjection of the GABAa agonist, muscimol, close to the M1 stimulation site, the late I waves (I_2, I_3) are mostly abolished (*red trace*); there is a small reduction in the I_1 wave and no obvious effect on the D wave. Averages of 150 sweeps, volleys recorded from the C3 spinal level. **b–d** Effects of muscimol injection in M1 on F5-M1 interaction. A single test (T) M1 shock was conditioned (C) by a single shock to the F5 division of PMv (*green*). Responses to the F5 shock alone are *orange* and to the M1 shock alone are *purple*. With a C–T interval of 0 ms, there was a marked facilitation of the I_3 wave. Twenty minutes after muscimol injection (**c**), this facilitation was considerably reduced, and it was abolished after 40 min (**d**). Averages of 100 sweeps. **e** Possible mechanisms explaining facilitation of late I waves (elements in *grey*), on the left of the diagram, represent the three classes of excitatory inputs to corticospinal neurons (CSNs): the D wave, the I_1 wave, and the later (I_2 and I_3) waves. A low-threshold inhibitory input pathway is also shown. These four inputs are all excited by stimulation within M1. The model proposes that the main excitatory input from F5 to M1 converges on the late interneuronal pathways in M1 giving rise to the I_2 and I_3 waves, thereby allowing F5 to influence I wave generation in M1 corticospinal neurons. Note that although these neurons project directly to hand motoneurons, this is probably not the case for those located in F5 (from Lemon 2008, with permission)

during twin-coil TMS studies in humans and show that the interactions between well-focused sites can be very large indeed, possibly because there is less concomitant inhibition (see Sect. 2.4.3).

Examination of the EMG response latency gave some clues as to its origin. We compared it with that evoked by direct stimulation of the pyramidal tract (PT) at the medullary level. The earliest EMG responses to PT stimulation will be those mediated by direct, CM connections (Olivier et al. 2001). We found that the EMG

responses evoked by *test* shocks to M1 (Fig. 2.4b) were typically around 3 ms longer than those from the PT.

What is the explanation? Stimulation of the motor cortex, even with single TMS or electrical shocks, results in high-frequency repetitive discharge of corticospinal neurons, which is highly synchronised into successive waves of descending activity in the corticospinal tract (Fig. 2.5a, e; see Di Lazzero et al. 2008). Intracortical stimuli act by discharging intracortical axons. The direct (D) wave results from direct activation of the axons of corticospinal neurons. Other axons that are excited feed into local interneuronal networks that lie upstream of the corticospinal neurons, and which lead to trans-synaptic excitation of them, generating a number of indirect waves (I_1, I_2, I_3 etc.; Fig. 2.5e) (Amassian et al. 1987; Ziemann and Rothwell 2000; Di Lazzaro et al. 2008). Each wave of activity is separated from the next by around 1–1.6 ms. Thus Cerri et al. (2003) speculated that the EMG responses to M1 stimulation are due to the accumulating depolarisation in spinal motoneurons, synchronised with the D and I wave inputs. However, the motoneurons are not actually discharged until the EPSPs generated by the I_2 or I_3 waves have arrived at the motoneurons.

As might be expected from this rather complex generation of the EMG response, the latency of the *conditioned* responses showed some considerable variation (Fig. 2.4c). The facilitation, by the conditioning PMv shock, of the different waves of activity generated by the test M1 shock could be expected to produce EMG responses ranging from those with latencies shorter than the test response (due to facilitation of the D or I_1 waves) to those with rather similar latencies (facilitation of the l_2 and I_3 waves): and this is what was found, but with a clear preference for responses reflecting discharge of motoneurons by the I_1 and especially by the I_2 waves (Cerri et al. 2003).

Examination of the EMG responses at different condition-test intervals confirmed the short time course of the PMv-M1 interaction. The first significant effects were observed at a condition-test (C-T) interval of 1 ms, and intervals up to 15 ms continued to show facilitation; at a C-T interval of 30 ms the conditioned response had returned to baseline (Cerri et al. 2003).

2.5.2 *Corticospinal and Motoneuron Responses in Anaesthetised Monkeys*

The significance of this short-latency interaction was clarified by a subsequent study, carried out in deeply anaesthetised macaques, in which the interaction between F5 and M1 was assessed by means of direct recording from the corticospinal tract and intracellularly from responding spinal motoneurons (Shimazu et al. 2004). These experiments showed that stimulation of macaque F5, which by itself evoked little or no detectable corticospinal output, could produce a robust modulation of motor outputs from M1. Thus, whereas single stimuli delivered to

M1 electrodes evoked the characteristic pattern of D and I waves (Fig. 2.5b, purple trace; see Sect. 2.5.1), single shocks delivered to F5 were ineffective (see orange trace in Fig. 2.5b) and even double shocks, with a 3 ms separation, evoked small I waves but no D wave, and only with high intensities.

However, when the test (T) M1 shock was conditioned (C) by single or double F5 shocks, there was strong facilitation of I_2 and I_3 waves from M1, but the D wave and I_1 waves remained unaffected (Fig. 2.5b, green trace). The facilitation of the late I waves was again observed with short C-T intervals, as in the EMG study. Although the conduction time from F5 to M1 is short (1–2 ms; Godschalk et al. 1984, Sect. 2.4.1 above), this would still allow ample time for activity generated by a shock to F5 to facilitate interneuronal circuits generating the later I_2 and I_3 waves.

Further evidence that it was these late waves that were important for the motor response was deduced by recording intracellularly from motoneurons innervating hand and forearm muscles. These recordings revealed no postsynaptic effects from single F5 shocks, but in contrast, the same stimuli produced a robust facilitation of EPSPs evoked from M1, whose onset closely followed the arrival of I_2 and I_3 waves at the spinal segment in which the recordings were made. The facilitation was particularly marked in hand muscle motoneurons, of which 92 % showed this facilitatory effect.

The key question posed by Shimazu et al. (2004) was: where was the site of interaction between F5 and M1? Three pieces of evidence were advanced to suggest that the interaction was within M1 itself. The first was that the short-latency of the interaction indicated a site close to F5, the second was that the time course of the interaction, which showed a characteristic waxing and waning of the facilitatory effect that fitted exactly with the timing of I waves originating from M1. The final piece of evidence was that after microinjection of the GABA-agonist muscimol in M1, the F5-induced facilitation of late I waves from M1 was completely abolished (green traces in Fig. 2.5b–d).

2.5.3 *Cortico-Cortical Circuit Activated During F5-M1 Interactions*

Shimazu et al. (2004) suggested that "the corticocortical pathways excited by F5 stimulation terminate preferentially on the cortical interneurons involved in generation of the late I waves, explaining why the D and I_1 waves were not facilitated to the same extent as the later I waves. The late I wave pathway is probably oligosynaptic, with conduction delays in the order of 2–4 ms. It is more susceptible to $GABA_A$ agonists such as diazepam and muscimol than the I_1 pathway, ⋯ (Ilic et al. 2002); this would explain why muscimol depressed the I_2 and I_3 components (Fig. 2.5a) and abolished their facilitation from F5" (see Fig. 2.5 b–d). Their proposed circuit is shown in Fig. 2.5e.

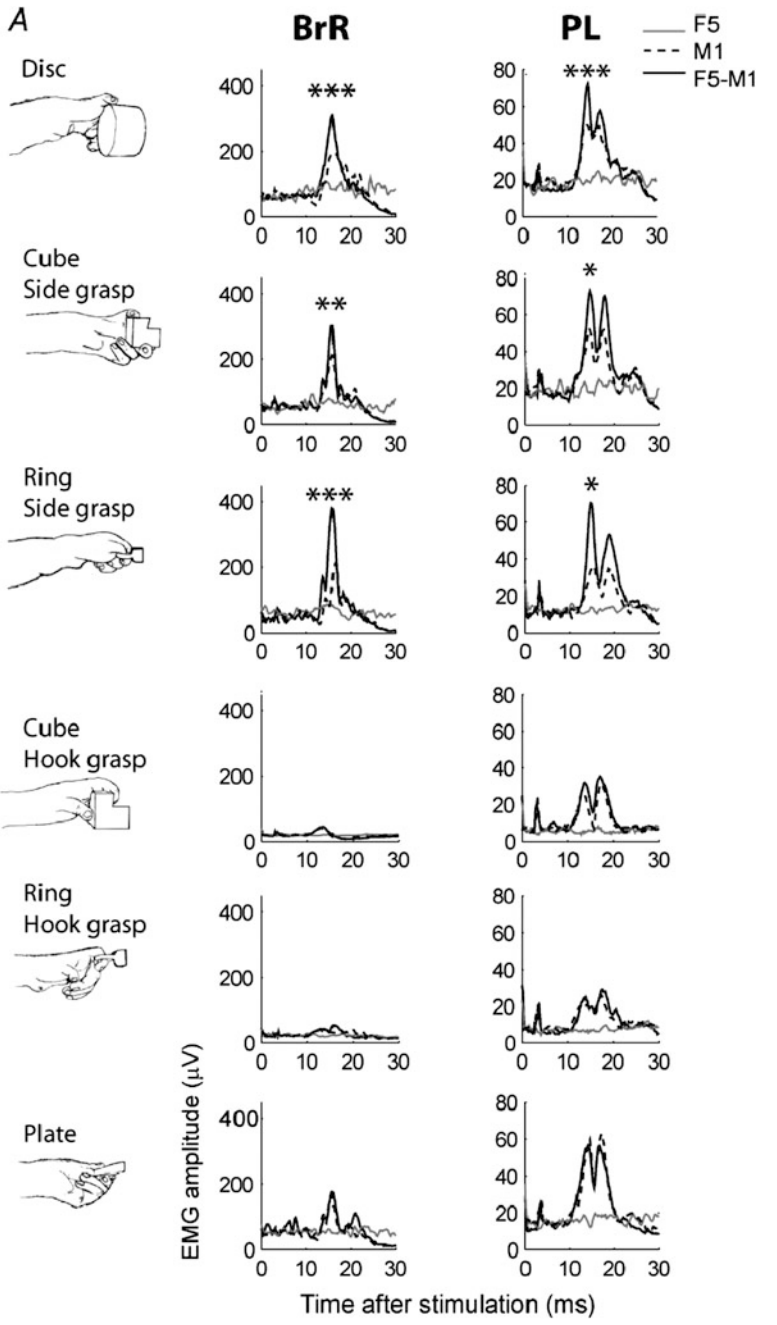
One potentially puzzling result of these studies was that if the number of shocks or stimulus intensity to F5 was increased, descending volleys and resulting motor responses could be observed. A clue to the answer was that the I waves evoked by these strong stimuli had fast conduction velocities ($\sim$80 m/s), that were identical to those for I waves evoked by M1 stimulation. Since we know that the cortico-spinal fibres derived from F5 itself are relatively slowly conducting (see Sect. 2.1 above), these I waves cannot have originated from F5, but probably resulted from intense excitation of the networks in M1 by cortico-cortical inputs activated by strong F5 stimulation. In other words, the later I waves resulting from F5 stimulation were actually conveyed in corticospinal neurons whose cell bodies were in M1. This has subsequently been shown by direct recording from single cortico-spinal neurons (Maier et al. in preparation). Further evidence for this mechanism comes from the finding that muscimol inactivation of the M1 hand area greatly reduces the I waves evoked by strong F5 stimulation (Shimazu et al. 2004).

2.6 Stimulus Evoked F5-M1 Interactions in the Awake, Behaving Monkey

Although the studies described above provided some useful insights into the potential circuitry underlying PMv-M1 interactions, they do not tell us how these structures interact during behaviourally relevant conditions. To address this issue, we applied the same F5-M1 stimulation protocols in awake monkeys trained to carry out a visuomotor reach-to-grasp task (Brochier et al. 2004; Prabhu et al. 2009). Once again, the electrode locations were chosen on the basis of previous rICMS mapping of the M1 and F5 hand areas. The EMG responses evoked by M1 test (T) stimulation were recorded from contralateral hand, digit and arm muscles during reach-to-grasp of visually presented objects, which were presented in a pseudo-random order at the beginning of each trial. Stimuli were delivered just as monkeys began to move, a few hundred ms before they first contacted the object.

Conditioning (C) stimulation of F5, at intensities that were subthreshold for any motor effects, caused considerable modulation (over twofold) of the test (T) EMG responses. The pattern of facilitation was specific. First, it was particularly evident at short C-T intervals. Second, this facilitation was only present in some, but not all muscles, and during reach-to-grasp of some, but not all objects. Modulation of responses was common in extrinsic and intrinsic muscles acting on the thumb and index finger. Finally, facilitation was found only for particular combinations of F5 electrodes.

Examples of the interaction effects produced by F5-M1 stimulation during the reach-to-grasp of six different objects are shown in Fig. 2.6. The responses shown are from two forearm muscles, brachioradialis (BrR) and palmaris longus (PL). F5 stimulation produced significant (* in Fig. 2.6) facilitation of both muscles during


A
BrR
PL
F5
M1
F5-M1
Disc
Cube
Side grasp
Ring
Side grasp
Cube
Hook grasp
Ring
Hook grasp
Plate
***
**
*
EMG amplitude (μV)
Time after stimulation (ms)

◀**Fig. 2.6** Grasp specificity of F5 conditioning of M1 stimulation and EMG activity during reach-to-grasp **a** averaged evoked EMG responses from brachioradialis (BrR) and Palmaris longus (PL) to F5 conditioning (C) (*grey* traces), M1 test (T) stimuli (*dashed* traces) and combined F5-M1 stimulation at C-T = 3.5 ms (*black* traces) during grasp of six different objects. Stimuli were delivered 50 ms just as the monkey reached to grasp to the objects. Wilcoxon's signed-rank test: * $P < 0.05$, ** $P < 0.001$, ***$P < 0.0001$. All figures are with 10 % outliers removed. Averages are of 23–67 trials per condition. Note that strong C-T (F5-M1) interactions were only obtained for grasp of some objects (*disc*, *cube* or *ring*), with side grasp, but not the others (from Prabhu et al. 2009, with permission)

reach-to-grasp of the disc, and of both a cube and a ring, when a side grip (object grasped between thumb and side of the index finger) was used. However, when a hook grip (involving only the index finger) was used to grasp either the ring or the cube, no facilitation was found. Finally, there was no facilitation of either muscle for grasp of the plate.

Unfortunately, the basis of this differential facilitation was unclear: there was no obvious relationship between either the level of EMG activity at the time the C-T stimuli were delivered, nor to the pattern of activity associated with the particular grasps tested. Clearly more work is needed here; the analysis might well be more straightforward if C-T stimuli were delivered during the 'observation period', when the monkey can see the object, but is still waiting for the cue to grasp it. In TMS studies of human volunteers, grasp-specific F5-M1 interactions are already clearly present in this period (Prabhu et al. 2007; Davare et al. 2008).

Interestingly, Prabhu et al. (2009) also reported signs of suppression: at later C-T intervals (1–6 ms), F5 stimulation caused significant suppression of the test M1 response. This raises the possibility that suppression of M1 outputs can be used to sculpt M1 outputs that ultimately help to shape the hand to grasp an object. In general, the results are in keeping with the concept that during visually guided grasp, F5 modulates corticospinal outputs from M1 in a muscle- and grasp-specific manner.

2.7 Are the Motor Responses Evoked by Stimulation of PMv also Mediated Through M1?

The lateral premotor subdivision of Brodmann area 6, was one of the earliest regions properly identified as giving rise to well-defined motor responses in the hand and digits when stimulated electrically (Leyton and Sherrington 1917), and this has been confirmed many times since (Kurata and Tanji 1986; Rizzolatti et al. 1988; Weinrich and Wise 1992; Godschalk et al. 1995). Using trains of intracortical stimuli (rICMS), the thresholds for exciting digit movements from PMv tend to be higher than in M1, but the responses are certainly very robust. Given the findings described above, it is of course interesting to question whether these

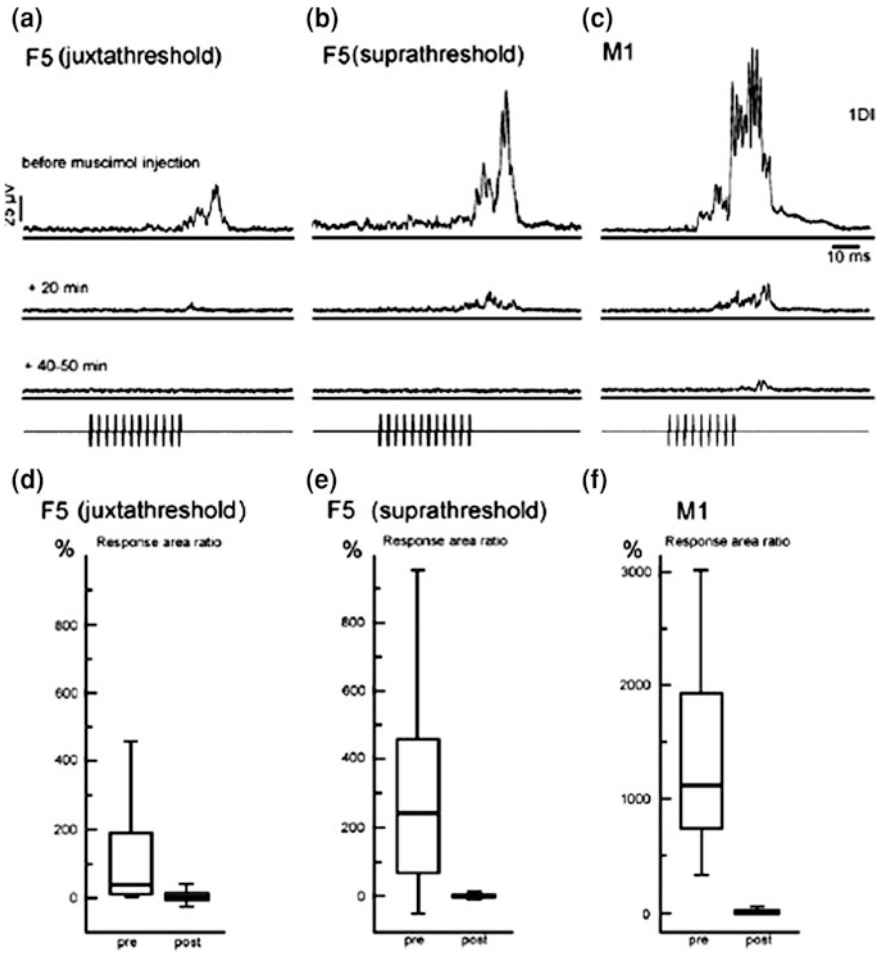


Fig. 2.7 Abolition of motor responses evoked by stimulation in F5 by muscimol injection in M1. **a–c** Average rectified EMG responses from an intrinsic hand muscle (1DI) evoked by rICMS (pulse train shown in *bottom* trace) before and after a microinjection of muscimol into the M1 hand area. **a** Averaged EMG response evoked by repetitive intracortical microstimulation (rICMS) in the F5 hand area at an intensity close to threshold (juxtathreshold) for evoking a response (12 pulses, 80 μA). **b** Responses evoked by rICMS in F5 at an intensity 25 % above threshold (suprathreshold; 12 pulses, 100 μA). **c** Responses evoked by rICMS in the M1 hand area (9 pulses, 45 μA). Control responses evoked before muscimol (**a–c**, *top* traces) were greatly reduced 20 min after the muscimol inactivation (*middle* traces). After 40–50 min (*bottom* traces), responses to F5 stimulation were completely abolished whereas those to M1 stimulation were very small. All averages are of 50 sweeps. **d–f** Quantitative analysis of decrease of EMG responses after muscimol injection in M1. Stimulation details are as in **a–c** Box plots show a decrease in the area ratio of the EMG responses evoked by rICMS before (pre) and after (post) (50 min after last injection of muscimol in the M1 hand area) injection in one monkey. The plots show the median (thick horizontal bar) data between the 25 and 75 % quartiles (box) and between 10 and 90 % (error bars) of the area of the EMG response normalised to the background level of EMG activity ('response area ratio'). Note the difference in the relative sizes of the EMG responses evoked from F5 and M1 (from Schmidlin et al. 2008, with permission)

motor responses might also depend upon the integrity of M1. We tested this by recording, from digit muscles, responses that were evoked by rICMS delivered to area F5, before, during and after temporary inactivation of the M1 hand area with microinjections of muscimol (Schmidlin et al. 2008). The study was carried out in lightly sedated macaques.

As Fig. 2.7 shows, muscimol injection in the M1 hand area not only greatly reduced EMG responses evoked from M1 with rICMS, but also reduced or abolished responses from F5, over a similar time course (20–50 min). Muscimol in M1 also reduced the level of background EMG activity in the contralateral hand (compare background EMG levels in Fig. 2.7b for example), and the hands was paretic for several hours after the injection. However, because EMG responses to direct activation of the corticospinal tract (using PT stimulation) were significantly less affected than the responses to F5 stimulation, it is unlikely that reduced motoneuronal excitability explained the loss of the evoked responses from F5. Finally, as in the Shimazu et al. (2004) study, muscimol injections in M1 greatly reduced the corticospinal volleys evoked by rICMS in F5. The results suggest that the motor effects evoked from F5 depend, at least in part, on cortico-cortical interactions with M1, leading to activation of M1 corticospinal outputs to hand muscles.

These findings are important first for the specific case of understanding the interactions between F5 and M1, but more generally, because they demonstrate that a characteristic property of one cortical area (ICMS in F5 producing digit movements at low-threshold) is actually dependent upon the integrity of another area (the hand representation of M1).

2.8 What About Reciprocal Projections from M1 to Area F5?

The function of the 'forward' projection from area F5 to M1 is at the heart of the concept of the 'visuomotor grasping circuit'. However, all of the anatomical studies of PMv-M1 connectivity have stressed the reciprocal nature of the connections between these structures. Indeed, Dum and Strick (2005) showed that the normalised strength and density of the interconnections between the M1 and PMv digit zones were rather similar, and originated in equal measure from deep and superficial laminae. On the basis of the anatomical origin, Dum and Strick (2005) considered that the two projections operated at an equivalent hierarchical level. Kraskov et al. (2011) found that responses in single M1 neurons to stimulation within F5 were equally common as F5 neurons responding to M1 stimulation.

The functions of the 'return' connections from M1 to F5 are still unknown, but they could be involved in updating both frontal and parietal areas as to the current state of the active motor network, and such a signal might be important in identifying the 'agency' of actions, allowing higher order structures to tag movement-related activity as self-generated or due to the actions of another. Also, these return connections would be required to update internal models about an object's physical

properties. Internal models will then allow prediction of the forces required in the subsequent manipulation of the same object (Loh et al. 2010).

2.9 Functional Considerations and Summary

The experimental studies reviewed here give some clues as to how PMv, from its nodal position in the visuomotor grasping circuit, might influence skilled grasp. The studies have stressed the importance of the cortico-cortical connections between PMv and M1, and have shown that these connections possess all the key characteristics to allow PMv to modulate grasp-related oputputs from M1.

- First, the connections allow fast interactions. This is important because we know that the grasping circuit is activated very rapidly by vision of grasping objects. Both monkey and human experiments indicate that grasp-related changes are already present around 100–150 ms after object presentation (Umilta et al. 2007; Prabhu et al. 2007).
- Second, the connections, at least when tested with electrical stimulation, are very powerful and allow M1 outputs to be deeply modulated.
- Third, in the awake monkey, F5 inputs can either facilitate or suppress M1 corticospinal outputs.
- Finally, the connections allow grasp-specific changes in M1 outputs, which is obvious importance in matching the grasp to the physical properties of the object.

There may be some interesting parallels between the PMv-M1 interactions described here and those reported for gain control of smooth pursuit eye movements (Tanaka and Lisberger 2001). The facilitation exerted by F5 on motor outputs from M1 may also act as a gain control system on these outputs; this could be part of a wider control system that helps to shape the pattern of activity across different hand muscles appropriate for grasp of specific objects.

This review has highlighted the point that the integrity of the M1 hand area is essential for the function of F5. However, all of these studies were done in intact, healthy monkeys. There is considerable evidence from the human and animal stroke literature (Chollet et al. 1991; Liu and Rouiller 1999; Nudo 1999; Frost et al. 2003; Dancause et al. 2005; Ward 2006; Ward and Frackowiak 2006) that after damage to M1, PMv can play a role in the longer term recovery of hand motor function. This is very different to the effects of acute inactivation of M1, as described by Schmidlin et al. (2008). Clearly long-term compensatory changes cannot involve the same interactions with M1, and must depend to some extent on plastic changes in the connections of PMv to other surviving motor areas (including PMd and the SMA) and subcortical and spinal changes, possibly including recruitment of reticulospinal (Zaaimi et al. 2012) and/or propriospinal systems (Borra et al. 2010).

The studies described in this review were all done in the macaque monkey model. However, the results obtained have constantly informed and prompted

parallel experiments in the human (Prabhu et al. 2007), especially those led by Davare and colleagues (Davare et al. 2008, 2009, 2010, 2011), which have also demonstrated a powerful interaction between PMv and M1 in the human brain that is strongly influenced by preparation to grasp visible objects. It is arguable whether we would be able to properly interpret the results of these non-invasive studies without the knowledge gained from the monkey research.

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References

Alstermark B, Pettersson LG, Nishimura Y, Yoshino-Saito K, Tsuboi F, Takahashi M, Isa T (2011) Motor command for precision grip in the macaque monkey can be mediated by spinal interneurons. J Neurophysiol 106:122–126

Amassian VE, Stewart M, Quirk GJ, Rosenthal JL (1987) Physiological basis of motor effects of a transient stimulus to cerebral cortex. Neurosurgery 20:74–93

Baker SN, Jackson A, Spinks R, Lemon RN (2001) Synchronization in monkey motor cortex during a precision grip task I. Task-dependent modulation in single-unit synchrony. J Neurophysiol 85:869–885

Belmalih A, Borra E, Contini M, Gerbella M, Rozzi S, Luppino G (2009) Multimodal architectonic subdivision of the rostral part (area F5) of the macaque ventral premotor cortex. J Comp Neurol 512:183–217

Borra E, Belmalih A, Gerbella M, Rozzi S, Luppino G (2010) Projections of the hand field of the macaque ventral premotor area F5 to the brainstem and spinal cord. J Comp Neurol 518:2570–2591

Boussaoud D, Tanne-Gariepy J, Wannier T, Rouiller EM (2005) Callosal connections of dorsal versus ventral premotor areas in the macaque monkey: a multiple retrograde tracing study. BMC Neurosci 6:67

Brochier T, Spinks RL, Umilta MA, Lemon RN (2004) Patterns of muscle activity underlying object-specific grasp by the macaque monkey. J Neurophysiol 92:1770–1782

Cerri G, Shimazu H, Maier MA, Lemon RN (2003) Facilitation from ventral premotor cortex of primary motor cortex outputs to macaque hand muscles. J Neurophysiol 90:832–842

Chollet F, DiPiero V, Wise RJS (1991) The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann Neurol 29:265–276

Dancause N, Barbay S, Frost SB, Plautz EJ, Chen D, Zoubina EV, Stowe AM, Nudo RJ (2005) Extensive cortical rewiring after brain injury. J Neurosci 25:10167–10179

Dancause N, Barbay S, Frost SB, Mahnken JD, Nudo RJ (2007) Interhemispheric connections of the ventral premotor cortex in a new world primate. J Comp Neurol 505:701–715

Davare M, Lemon R, Olivier E (2008) Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans. J Physiol 586:2735–2742

Davare M, Montague K, Olivier E, Rothwell JC, Lemon RN (2009) Ventral premotor to primary motor cortical interactions during object-driven grasp in humans. Cortex 45:1050–1057

Davare M, Rothwell JC, Lemon RN (2010) Causal connectivity between the human anterior intraparietal area and premotor cortex during grasp. Curr Biol 20:176–181

Davare M, Kraskov A, Rothwell JC, Lemon RN (2011) Interactions between areas of the cortical grasping network. Curr Opin Neurobiol 21:565–570

Di Lazzaro V, Ziemann U, Lemon RN (2008) State of the art: physiology of transcranial motor cortex stimulation. Brain Stimul 1:345–362

Douglas RJ, Martin KA (2004) Neuronal circuits of the neocortex. Annu Rev Neurosci 27: 419–451

Dum RP, Strick PL (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. J Neurosci 11:667–689

Dum RP, Strick PL (2005) Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. J Neurosci 25:1375–1386

Frost SB, Barbay S, Friel KM, Plautz EJ, Nudo RJ (2003) Reorganization of remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery. J Neurophysiol 89:3205–3214

Gerbella M, Belmalih A, Borra E, Rozzi S, Luppino G (2011) Cortical connections of the anterior (F5a) subdivision of the macaque ventral premotor area F5. Brain Struct Funct 216:43–65

Gharbawie OA, Stepniewska I, Qi H, Kaas JH (2011) Multiple parietal-frontal pathways mediate grasping in macaque monkeys. J Neurosci 31:11660–11677

Glickstein M, May JG III, Mercier BE (1985) Corticopontine projection in the macaque: the distribution of labelled cortical cells after large injections of horseradish peroxidase in the pontine nuclei. J Comp Neurol 235:343–359

Godschalk M, Lemon RN, Kuypers HGJM, Ronday HK (1984) Cortical afferents and efferents of monkey post- arcuate area: an anatomical and electrophysiological study. Exp Brain Res 56:410–424

Godschalk M, Mitz AR, Van Duin B, Van der Burg H (1995) Somatotopy of monkey premotor cortex examined with microstimulation. Neurosci Res 23:269–279

Haaxma R, Kuypers H (1974) Role of occipito-frontal cortico-cortical connections in visual guidance of relatively independent hand and finger movements in rhesus monkeys. Brain Res 71:361–366

Halsband V, Passingham RE (1982) The role of premotor and parietal cortex in the direction of action. Brain Res 240:368–372

He SQ, Dum RP, Strick PL (1993) Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. J neurosci 13:952–980

Ilic TV, Meintzschel F, Cleff U, Ruge D, Kessler KR, Ziemann U (2002) Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. J Physiol (Lond) 545:153–167

Isa T, Ohki Y, Alstermark B, Petterson LG, Sasaki S (2007) Direct and indirect cortico-motoneuronal pathways and control of hand/arm movements. Physiology 22:145–152

Jeannerod M, Arbib MA, Rizzolatti G, Sakata H (1995) Grasping objects: the cortical mechanisms of visuomotor transformation. Trends Neurosci 18:314–320

Jenny AB, Inukai J (1983) Principles of motor organization of the monkey cervical spinal cord. J Neurosci 3:567–575

Jones EG, Wise SP (1977) Size, laminar and columnar distribution of efferent cells in the sensory-motor cortex of monkeys. J Comp Neurol 175:391–438

Kraskov A, Dancause N, Quallo MM, Shepherd S, Lemon RN (2009) Corticospinal neurons in macaque ventral premotor cortex with mirror properties: a potential mechanism for action suppression? Neuron 64:922–930

Kraskov A, Prabhu G, Quallo MM, Lemon RN, Brochier T (2011) Ventral premotor-motor cortex interactions in the macaque monkey during grasp: response of single neurons to intracortical microstimulation. J Neurosci 31:8812–8821

Kurata K, Tanji J (1986) Premotor cortex neurons in macaques: activity before distal and proximal forelimb movements. J Neurosci 6:403–411

Lemon RN (2008) Descending pathways in motor control. Annu Rev Neurosci 31:195–218

Leyton SSF, Sherrington CS (1917) Observations on the excitable cortex of the chimpanzee, orangutan and gorilla. Q J Exp Physiol 11:135–222

Liu Y, Rouiller EM (1999) Mechanisms of recovery of dexterity following unilateral lesion of the sensorimotor cortex in adult monkeys. Exp Brain Res 128:149–159

Loh MN, Kirsch L, Rothwell JC, Lemon RN, Davare M (2010) Information about the weight of grasped objects from vision and from internal models interacts within the primary motor cortex. J Neurosci 30:6984–6990

Maier MA, Armand J, Kirkwood PA, Yang HW, Davis JN, Lemon RN (2002) Differences in the corticospinal projection from primary motor cortex and supplementary motor area to macaque upper limb motoneurons: an anatomical and electrophysiological study. Cereb Cortex 12:281–296

Muakkassa K, Strick P (1979) Frontal lobe inputs to primate motor cortex: evidence for somatotopically organized premotor areas. Brain Res 177:176–182

Nudo RJ (1999) Recovery after damage to motor cortical areas. Curr Opin Neurobiol 9:740–747

Olivier E, Baker SN, Nakajima K, Brochier T, Lemon RN (2001) Iinvestigation into non-monosynaptic corticospinal excitation of macaque upper limb single motor units. J Neurophysiol 86:1573–1586

Pandya DN, Kuypers HGJM (1969) Cortico-cortical connections in the Rhesus monkey. Brain Res 13:13–36

Prabhu G, Voss M, Brochier T, Cattaneo L, Haggard P, Lemon R (2007) Excitability of human motor cortex inputs prior to grasp. J Physiol 581:189–201

Prabhu G, Shimazu H, Cerri G, Brochier T, Spinks RL, Maier MA, Lemon RN (2009) Modulation of primary motor cortex outputs from ventral premotor cortex during visually-guided grasp in the macaque monkey. J Physiol 587:1057–1069

Raos V, Umilta MA, Murata A, Fogassi L, Gallese V (2006) Functional properties of grasping-related neurons in the ventral premotor area F5 of the macaque monkey. J Neurophysiol 95:709–729

Rizzolatti G, Luppino G (2001) The cortical motor system. Neuron 31:889–901

Rizzolatti G, Camarda R, Fogassi L, Gentilucci M, Luppino G, Matelli M (1988) Functional organization of inferior area 6 in the macaque monkey II. area F5 and the control of distal movements. Exp Brain Res 71:491–507

Rouiller EM, Babalian A, Kazennikov O, Moret V, Yu XH, Wiesendanger M (1994) Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. Exp Brain Res 102:227–243

Sakai H, Woody CD (1988) Relationships between axonal diameter, soma size, and axonal conduction velocity of HRP-filled, pyramidal tract cells of awake cats. Brain Res 460:1–7

Sasaki S, Isa T, Pettersson LG, Alstermark B, Naito K, Yoshimura K, Seki K, Ohki Y (2004) Dexterous finger movements in primate without monosynaptic corticomotoneuronal excitation. J Neurophysiol 92:3142–3147

Schmidlin E, Brochier T, Maier MA, Kirkwood PA, Lemon RN (2008) Pronounced reduction of digit motor responses evoked from macaque ventral premotor cortex after reversible inactivation of the primary motor cortex hand area. J Neurosci 28:5772–5783

Shimazu H, Maier MA, Cerri G, Kirkwood PA, Lemon RN (2004) Macaque ventral premotor cortex exerts powerful facilitation of motor cortex outputs to upper limb motoneurones. J Neurosci 24:1200–1211

Stein JF, Glickstein M (1992) Role of the cerebellum in visual guidance of movement. Physiol Rev 72:967–1017

Tanaka M, Lisberger SG (2001) Regulation of the gain of visually guided smooth-pursuit eye movements by frontal cortex. Nature 409:191–194

Tokuno H, Nambu A (2000) Organization of nonprimary motor cortical inputs on pyramidal and nonpyramidal tract neurons of primary motor cortex: an electrophysiological study in the macaque monkey. Cereb Cortex 10:58–68

Umilta MA, Brochier TG, Spinks RL, Lemon RN (2007) Simultaneous recording of macaque premotor and primary motor cortex neuronal populations reveals different functional contributions to visuomotor grasp. J Neurophysiol 98:488–501

Vigneswaran G, Kraskov A, Lemon RN (2011) Large identified pyramidal cells in macaque motor and premotor cortex exhibit "thin spikes": implications for cell type classification. J Neurosci 31:14235–14242

Ward NS (2006) The neural substrates of motor recovery after focal damage to the central nervous system. Arch Phys Med Rehabil 87:S30–S35

Ward NS, Frackowiak RS (2006) The functional anatomy of cerebral reorganisation after focal brain injury. J Physiol Paris 99:425–436

Weinrich M, Wise SP (1982) The premotor cortex of the monkey. J Neurosci 2:1329–1345

Zaaimi B, Edgley SA, Soteropoulos DS, Baker SN (2012) Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. Brain 135:2277–2289

Ziemann U, Rothwell JC (2000) I-waves in motor cortex. J Clin Neurophysiol 17:397–405

Part II
Assessment and Modulation of Cortical Connectivity using Non-Invasive Brain Stimulation in Human

Chapter 3
Intracortical Circuits and Their Interactions in Human Primary Motor Cortex

Zhen Ni and Robert Chen

Abstract The human primary motor cortex (M1) works in association with other motor-related brain areas in the planning and execution of movements. Transcranial magnetic stimulation (TMS) is a widely used noninvasive brain stimulation technique and TMS studies have contributed significantly to our knowledge of motor cortical physiology. Single-pulse TMS activates the facilitatory interneurons in M1 and produces descending corticospinal volleys in the spinal cord, resulting in motor evoked potential in the target muscle. There are different inhibitory and facilitatory intracortical circuits within the M1. The excitability of M1 is also modulated by interhemispheric inputs from the contralateral hemisphere and by inputs from premotor cortex, parietal cortex, cerebellum, and muscle afferents. The balance and interactions among the intracortical circuits determine the final motor cortical output. Moreover, the intracortical circuits are highly interconnected and the interactions among intracortical circuits can be investigated by a triple-pulse TMS paradigm.

Abbreviations

CBI	Cerebellar inhibition
CS	Conditioning stimulus
D-wave	Direct wave
GABA	Gamma-aminobutyric acid
I-wave	Indirect wave

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ICF	Intracortical facilitation
IHF	Interhemispheric facilitation
ISI	Interstimulus interval
LAI	Long-latency afferent inhibition
LICI	Long-interval intracortical inhibition
LIHI	Long-latency interhemispheric inhibition
M1	Primary motor cortex
MEP	Motor evoked potential
SAI	Short-latency afferent inhibition
SICF	Short-interval intracortical facilitation
SICI	Short-interval intracortical inhibition
SIHI	Short-latency interhemispheric inhibition
SP	Silent period
TMS	Transcranial magnetic stimulation
TS	Test stimulus

3.1 Introduction

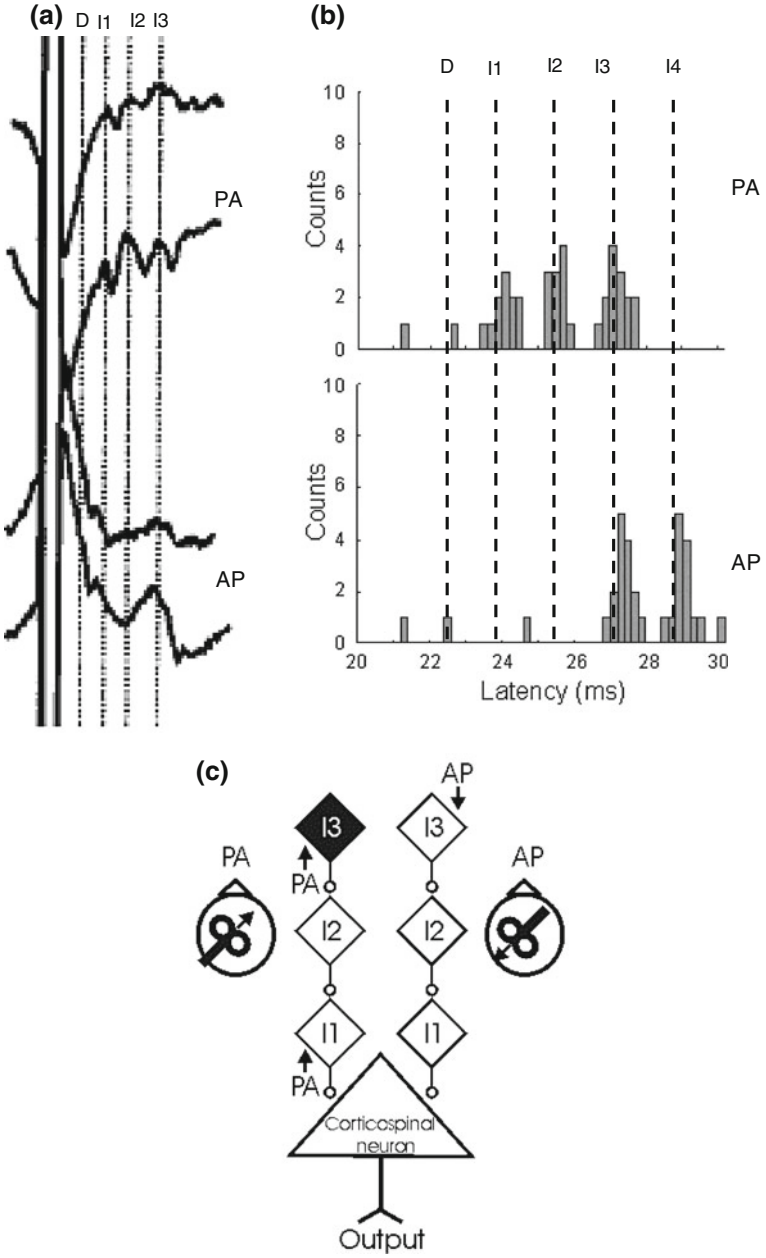
The human primary motor cortex (M1), usually identified as Brodmann area 4, is located in the dorsal part of the precentral gyrus and the anterior bank of the central sulcus. The M1 contains large corticospinal neurons known as Betz cells which send long axons down the spinal cord to synapse onto alpha motor neurons which connect to the target muscles. The M1 works in association with other motor-related brain areas in the planning and execution of movements. Transcranial magnetic stimulation (TMS) is a widely used noninvasive technique to study ongoing neural activity in the human cortex. When TMS is applied to the M1 with sufficient intensity, a motor evoked potential (MEP) can be recorded in the target muscle (Hallett 2007). The MEP size largely depends on the motor cortical and spinal excitability at the time of TMS delivery, which is dynamically modulated by excitation and inhibition within the stimulated area. There are complex neural networks involving inhibitory and facilitatory circuits within the M1 and between other motor-related cortical areas and the M1. The balance and interactions between these inhibitory and facilitatory circuits determine the final output from the M1 (Hallett 2007; Chen et al. 2008). Using paired-pulse TMS, various inhibitory and facilitatory intracortical circuits have been identified using different experimental paradigms. In addition to the modulation of motor cortical output, these intracortical circuits are also highly interconnected. The recently developed triple-pulse TMS paradigm has been used to explore interactions among these intracortical circuits. This chapter reviews the current knowledge of the functional organization of the intracortical circuits in the motor cortical network.

3.2 Intracortical Circuits for I-Wave Generations

Corticospinal neurons are among the largest neurons in the brain and are located in layer V of cerebral cortex. They receive inputs from facilitatory interneurons in the M1 (Patton and Amassian 1954). Single-pulse TMS of the M1 elicits a series of periodic, high frequency descending corticospinal waves termed indirect (I)-waves (Fig. 3.1a, 3.1b). The interval between these waves is consistent with the synaptic delay for the activation of facilitatory interneurons to corticospinal neurons (Di Lazzaro et al. 2004). The multiple I-waves are classified as early (e.g., I1) or late (e.g., I3) with respect to their latencies compared to the direct (D)-wave. The D-wave can be recruited by transcranial electrical stimulation of the M1 which activates the corticospinal neurons directly. The amplitude and the number of I-waves recruited reflect the activity of the facilitatory interneurons and this largely depends on the TMS intensity and current direction used. Recordings of corticospinal waves from spinal epidural electrodes have shown that TMS that induce posterior–anterior current in the brain generates early I-waves at slightly superthreshold intensities. With higher intensities, the early I-waves increase in size and are followed by late I-waves (Di Lazzaro et al. 1998a) (Fig. 3.1a). In contrast, anterior–posterior current predominantly recruits late I-waves, whereas lateral-medial current preferentially recruits the D-wave (Day et al. 1989; Sakai et al. 1997; Di Lazzaro et al. 2001). In addition, the I-waves can also be examined by analyzing the changes in firing probability of single motor units after TMS (Hanajima et al. 1998; Ni et al. 2011a) (Fig. 3.1b). Using single motor unit recording, it has been reported that late I-waves produced by posterior–anterior and anterior–posterior current directions have different sensitivities to the inhibitory effects produced by sensory afferent input, suggesting that TMS with these two current directions may produce late I-waves with the same latency but are due to activation of different cortical facilitatory circuits (Ni et al. 2011a). Figure 3.1c shows a possible model of I-wave generation based on these studies.

3.3 Intracortical Circuits Investigated Using a Paired-Pulse TMS Paradigm

A paired-pulse TMS paradigm involves a conditioning stimulus (CS) followed by a test stimulus (TS), and the effects are compared to that of the TS alone. Many intracortical circuits have been identified.


(a)
D I1 I2 I3
PA
AP
(b)
D I1 I2 I3 I4
Counts
PA
AP
Latency (ms)
(c)
PA
AP
I3
I2
I1
Corticospinal neuron
Output

◀**Fig. 3.1** Cortical circuits activated by different current directions. TMS with PA current generates early and late I-waves, while TMS with AP current predominantly generates late I-waves (I3-, I4-waves). **a** Example recordings of descending waves. **b** Example recordings of single motor unit. The dash lines show the latencies for D-wave and I-waves. The *first* and *third rows* in panel a show descending wave recordings with low TMS intensity (active motor threshold). The *second* and *fourth rows* show those with higher TMS intensity (active motor threshold + 30 % of stimulator output). **c** Model of the possible mechanism for I-wave generation with different current directions. The *triangle* indicates corticospinal neuron which produces output to the spinal motor neurons. The *diamonds* indicate facilitatory interneurons in the primary motor cortex that generate I1-, I2-, and I3-waves (to simplify the figure, neurons beyond those mediating the I3-wave generation are omitted). Only the I1-wave generating neuron connects directly with the corticospinal neuron. *PA* directed current activates both early and late I-wave generating neurons while AP directed current only activates late I-wave generating neuron. Note that, the I3-wave generating neurons activated by the *PA* and *AP* directed currents may be different and they are shown in *different colors* (*black* and *white*, respectively). *AP* anterior posterior, *D-wave* direct wave, *I-wave* indirect wave, *PA* posterior-anterior, and *TMS* transcranial magnetic stimulation. Modified from Di Lazzaro et al. (2001) and Ni et al. (2011a)

3.3.1 Short-Interval Intracortical Inhibition and Intracortical Facilitation

Short-interval intracortical inhibition (SICI) is elicited when a subthreshold CS is followed by a suprathreshold TS at an interstimulus interval (ISI) of 1–6 ms (Kujirai et al. 1993) (Fig. 3.2a, b). Although the subthreshold CS is not sufficient to discharge the corticospinal neurons (Fig. 3.2a), it activates the inhibitory interneurons in the M1, which produce inhibitory effects on the corticospinal neurons. Studies using epidural recordings have shown that SICI inhibits the late I-waves but not the early I-waves (Nakamura et al. 1997; Di Lazzaro et al. 1998b). SICI has been extensively investigated and is widely regarded as a main inhibitory system in the M1 (Kujirai et al. 1993; Nakamura et al. 1997; Di Lazzaro et al. 1998b). However, SICI may not represent a single inhibitory mechanism. There are two phases of SICI, peaking at ISIs of ~ 1 ms and 2.5 ms, respectively. SICI at 2.5 ms is likely mediated by gamma-aminobutyric acid type A ($GABA_A$) receptors because drugs that enhance $GABA_A$ increase SICI (Ziemann et al. 1996a). It has been proposed that SICI at 1 ms is due to the refractoriness of the cortical neurons (Fisher et al. 2002). However, SICI at 1 ms increases when the MEP size induced by TS is raised from 0.2 to 1 mV, suggesting that synaptic inhibition also contributes to SICI at 1 ms because a stronger TS should activate more corticospinal neurons and overcome the refractory period, which should lead to less inhibition (Roshan et al. 2003). In addition to the involvement of multiple inhibitory mechanisms, SICI is not due to pure inhibition but it reflects the balance between inhibition and facilitation. The resultant inhibition represents a complex interplay of the effects of CS and TS (Ilic et al. 2002; Roshan et al. 2003; Butefisch et al. 2003). The relationship between the degree of SICI and CS intensity is a U-shaped curve (Kujirai et al. 1993; Ziemann et al. 1996c; Chen et al. 1998; Ilic et al. 2002; Wagle-Shukla et al. 2009). An example is shown in Fig. 3.2c. At low

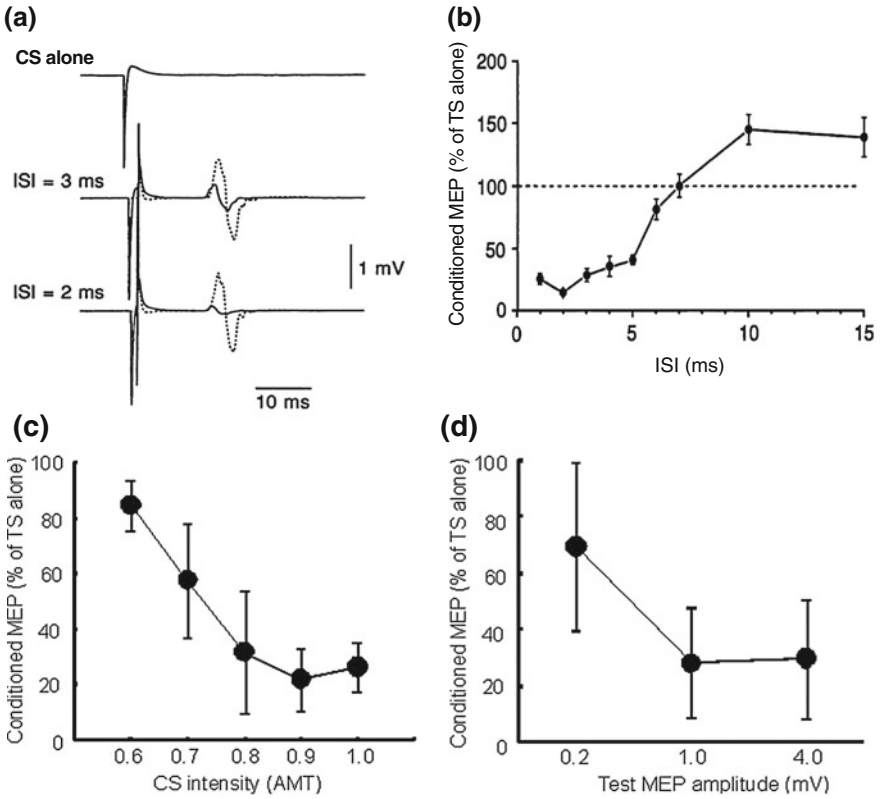


Fig. 3.2 Demonstration of short-interval intracortical inhibition and the effects of different stimulus parameters. **a** Example of recordings for SICI. The *first row* shows absence of MEP to the subthreshold CS given alone. The *second* and *third rows* show MEP induced by paired-pulse TMS (*solid line*) at ISI of 3 (*second row*) and 2 ms (*third row*). The *dash line* shows MEP induced by TS alone. **b** SICI is elicited with subthreshold CS followed by superthreshold TS at ISIs of 1–6 ms. ICF is elicited at ISIs of 10 and 15 ms. Data obtained from 10 subjects. **c** SICI tested at ISI of 3 ms with TS set at the intensity able to generate ~1 mV MEP. With increasing CS intensity from 0.6–0.9 AMT, SICI increases. On the other hand, with further increase in CS intensity from 0.9 to 1.0 AMT, SICI decreases. Data obtained from six subjects. **d** SICI tested at ISI of 3 ms with CS set at 0.8 resting motor threshold. Test MEP amplitudes were ~0.2, 1.0, 4.0 mV. Peak SICI occurred at TS intensity able to generate ~1 mV MEP. Data obtained from 11 subjects. Ordinate in **b**, **c**, **d** indicates the conditioned MEP amplitude. It is normalized as a percentage of the mean test MEP amplitude. Values above 100 % indicate facilitation and those below 100 % indicate inhibition. Error bars represent standard deviation. *AMT* active motor threshold; *CS* conditioning stimulus, *ICF* intracortical facilitation, *ISI* interstimulus interval, *MEP* motor evoked potential, *SICI* short interval intracortical inhibition, *and TS* test stimulus. Modified from Kujirai et al. (1993) and Wagle-Shukla et al. (2009)

CS intensities, increasing the CS intensity leads to greater SICI which can be explained by the increasing recruitment of inhibitory interneurons (SICI mediating neurons). Further increase in CS intensity leads to the reduction of inhibition and

eventually causes facilitation, possibly due to the recruitment of facilitatory circuits at high CS intensities (Kujirai et al. 1993; Peurala et al. 2008). Figure 3.2d shows the relationship between SICI and TS intensity that also manifests as a U-shaped curve with peak inhibition occurring at TS intensity adjusted to generate ~1 mV MEP in hand muscle (Sanger et al. 2001; Daskalakis et al. 2002; Ilic et al. 2002; Wagle-Shukla et al. 2009). Reduction of SICI at low TS intensity may be explained by the predominance of early I-waves such as the I1-wave with small MEPs (Di Lazzaro et al. 1998a), which are less sensitive to SICI than late I-waves (Di Lazzaro et al. 1998b). Decreased SICI at high TS intensity may be due to recruitment of corticospinal neurons that are spatially distant from the SICI mediating neurons activated by CS (Sanger et al. 2001; Daskalakis et al. 2002). Therefore, SICI is a complex measure and the results from SICI studies should be interpreted carefully taking into account the important effect of different stimulus parameters.

Intracortical facilitation (ICF) can be elicited with a similar protocol as SICI but at longer ISIs (Fig. 3.2b). The typical ISIs for eliciting ICF are 6–30 ms (Kujirai et al. 1993). The mechanisms mediating ICF remain unclear (Di Lazzaro et al. 2006). Pharmacological studies suggested that excitatory glutamatergic interneurons in M1 may be involved in ICF (Ziemann 2004). However, subcortical and spinal activities may also influence ICF because epidural recordings show that ICF is not associated with increased I-wave amplitudes (Di Lazzaro et al. 2006).

3.3.2 Long-Interval Intracortical Inhibition and Silent Period

With a suprathreshold CS applied 50–200 ms prior to the TS, the test MEP is inhibited. This type of inhibition is referred to as long-interval intracortical inhibition (LICI) (Valls-Solé et al. 1992; Wassermann et al. 1996; Sanger et al. 2001). Several lines of evidence suggest that the neural circuits mediating LICI and SICI are different. First, pharmacological studies have shown that LICI is likely mediated by $GABA_B$ receptors (Werhahn et al. 1999; McDonnell et al. 2006; Müller-Dahlhaus et al. 2008), while SICI is likely mediated by $GABA_A$ receptors (Ziemann et al. 1996a). Second, LICI decreases with increasing TS intensity (Sanger et al. 2001; Udupa et al. 2010) while the relationship between SICI and TS intensity shows a U-shaped curve. In addition, if TMS is applied during voluntary contraction a period of suppression in muscle activity can be recorded after MEP. This is referred to as the silent period (SP). Similarly to LICI, the later part of the SP is due to activation of cortical inhibitory circuits mediated by $GABA_B$ receptors (Siebner et al. 1998; Werhahn et al. 1999) while the early part of the SP may be related to spinal inhibitory mechanisms (Fuhr et al. 1991). Changes in the level of voluntary contraction do not significantly alter the length of the SP (Inghilleri et al. 1993).

3.3.3 Short-Interval Intracortical Facilitation

Short-interval intracortical facilitation (SICF) can be elicited by a suprathreshold first stimulus followed by a second stimulus at suprathreshold (Tokimura et al. 1996) or resting motor threshold level (Ziemann et al. 1998a). SICF occurs at three distinct phases with ISIs of around 1.5, 2.9, and 4.5 ms (Ziemann et al. 1998a; Chen and Garg 2000). No facilitation is observed if electrical stimulation is used for the second stimulus, suggesting that SICF originates at the cortical level (Ziemann et al. 1998a). The cortical nature of SICF has been confirmed by epidural recordings showing that the amplitude of I-waves generated by SICF in paired-pulse trials was more than the sum of I-waves generated by two stimuli given separately (Di Lazzaro et al. 1999). Because the effective ISIs for SICF coincide with the period of I-wave generations, SICF is likely related to the summation of different I-waves on the same corticospinal neurons (Ziemann and Rothwell 2000; Ilic et al. 2002). Voluntary contraction has only minor effects on SICF (Ziemann et al. 1998b). Administration of benzodiazepines that enhance the effects of $GABA_A$ decreases SICF, suggesting that GABAergic activity may be involved in SICF (Ziemann et al. 1996b). The TMS intensity and ISI for eliciting SICF partly overlap with those for eliciting SICI. This leads to the contamination of SICI by SICF and may explain why SICI decreases at higher CS intensities (Peurala et al. 2008) (Fig. 3.2c).

3.3.4 Interhemispheric Inhibition and Facilitation

Interhemispheric inhibition (IHI) is measured by delivering CS to the M1 followed by TS to the contralateral M1. Both CS and TS are suprathreshold. This inhibition is likely produced by interhemispheric excitatory pathways which run through the corpus callosum and synapse onto local inhibitory circuits in the target M1 (Ferbert et al. 1992b; Wahl et al. 2007; Ni et al. 2009). IHI is most pronounced at ISIs of $\sim$10 and $\sim$50 ms and they are referred to as short-and long-latency IHI (SIHI and LIHI) (Chen et al. 2003; Ni et al. 2009). Figure 3.3 shows that besides the interaction between the homologous M1s, IHI, especially LIHI, represents a widespread inhibitory system projecting from various motor-related cortical areas to the contralateral M1. These cortical areas include the dorsolateral prefrontal cortex, dorsal premotor cortex, and somatosensory cortex (Ni et al. 2009). Pharmacological studies suggest that LIHI is mediated by post-synaptic $GABA_B$ receptors, while the transmitter system mediating SIHI remains unknown (Irlbacher et al. 2007).

Interhemispheric facilitation (IHF) is elicited by a similar paired-pulse TMS paradigm as IHI but can only be observed with specific stimulus parameters. IHF between homologous M1s requires small test MEPs with slight voluntary contraction of the target muscle. IHF only occurs with a TS delivered in the anterior–posterior

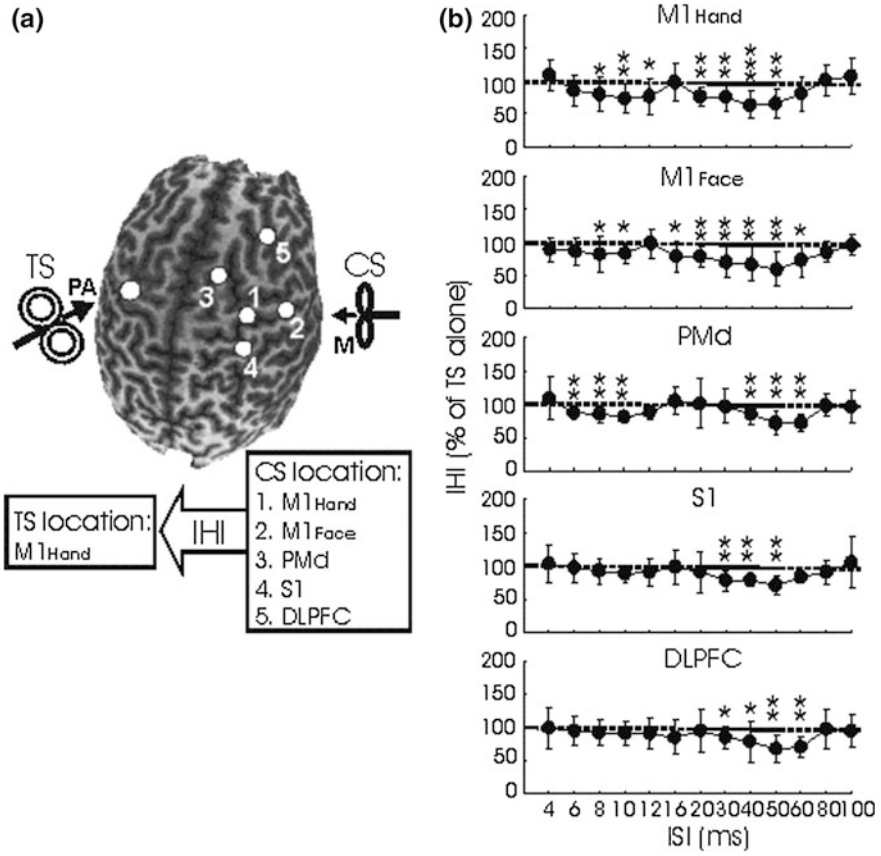


Fig. 3.3 Short-and long-latency interhemispheric inhibition. **a** Experimental setup. CS was applied to one of the different sites in the right hemisphere shown as *five white dots*. They are $M1_{Hand}$ (1), $M1_{Face}$ (2), PMd (3), S1 (4), and DLPFC (5). TS was applied to the hand representation (shown as *white dot*) of the left M1. **b** The time courses of IHI (group data from 12 subjects) from five different cortical areas to the contralateral M1. The abscissa indicates the ISI. The ordinate indicates the amplitude of conditioned MEP as a percentage of the MEP amplitude from TS alone. The *dashed lines* indicate the MEP amplitude generated by TS alone (100 %). Values below 100 % represent inhibition and values above 100 % represent facilitation. There are two phases of IHI with maximum inhibition at ISIs of $\sim$10 and $\sim$50 ms for $M1_{Hand}$, $M1_{Face}$, and PMd. For S1 and DLPFC, the early phase of IHI is absent and only the late phase is evident. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared to TS alone. *CS* conditioning stimulus, *DLPFC* dorsolateral prefrontal cortex, *IHI* interhemispheric inhibition, *ISI* interstimulus interval, *M1* primary motor cortex, $M1_{Face}$ facial muscle representation in M1, $M1_{Hand}$ hand muscle representation in M1, *MEP* motor evoked potential, *PMd* dorsal premotor cortex, *S1* somatosensory cortex, *and TS* test stimulus. Modified from Ni et al. (2009)

current direction and with CS of relatively low intensity (5–10 % above active motor threshold). The ISI required for facilitation is 4–5 ms (Hanajima et al. 2001). Further investigations showed that IHF can also be induced by CS over the dorsal premotor

cortex with lower intensity (0.6 or 0.8 of active motor threshold) at ISIs of 6 or 8 ms (Baumer et al. 2006).

3.3.5 Afferent Inhibition

Sensory afferent input generated by electrical peripheral nerve stimulation inhibits the contralateral M1. Short-latency afferent inhibition (SAI) is elicited if median nerve stimulation precedes M1 TMS at ISIs around the latency of N20 component of the somatosensory evoked potential (Tokimura et al. 2000). SAI lasts for 7–8 ms with median nerve stimulation. Epidural recordings demonstrated that late I-waves are predominately inhibited by SAI while early I-waves are not affected (Tokimura et al. 2000). A study using surface EMG and single motor unit recordings showed that late I-waves induced by posterior–anterior current direction are more inhibited by SAI than those induced by anterior–posterior current direction (Ni et al. 2011a). Pharmacological study showed that cholinergic pathways are involved in generating SAI (Di Lazzaro et al. 2000). Moreover, SAI is reduced by lorazepam, suggesting that GABAergic circuits may also be involved (Di Lazzaro et al. 2005).

Long-latency afferent inhibition (LAI) is elicited when electrical median nerve stimulation is applied before TMS at ISIs around 200 ms (Chen et al. 1999). It likely involves changes in cortical excitability because F-wave recordings showed no change in spinal excitability (Chen et al. 1999). The neurotransmitters mediating LAI are not known.

3.3.6 Cerebellar Inhibition

Cerebellar inhibition (CBI) refers to the phenomenon that stimulation over one cerebellar hemisphere suppresses the MEP elicited by subsequent TMS of the contralateral M1 at ISIs of 5–7 ms. CBI is thought to be mediated by activation of cerebellar Purkinje cells by cerebellar stimulation. The Purkinje cells inhibit the M1 via a disynaptic pathway through relays in the deep cerebellar nuclei and in the ventral lateral thalamus (Ugawa et al. 1995; Pinto and Chen 2001).

3.3.7 Inputs from Premotor Cortex and Parietal Cortex

Inputs from other cortical areas such as the premotor and parietal cortices also modulate M1 excitability. CS applied 3–5 cm anterior to the M1 or 6 cm anterior to the vertex inhibits the TS applied to M1 at short latency. The largest effect was seen at ISI of 6 ms with CS intensity of 90 % active motor threshold. Interestingly, increasing the CS intensity to 120 % active motor threshold produced facilitation

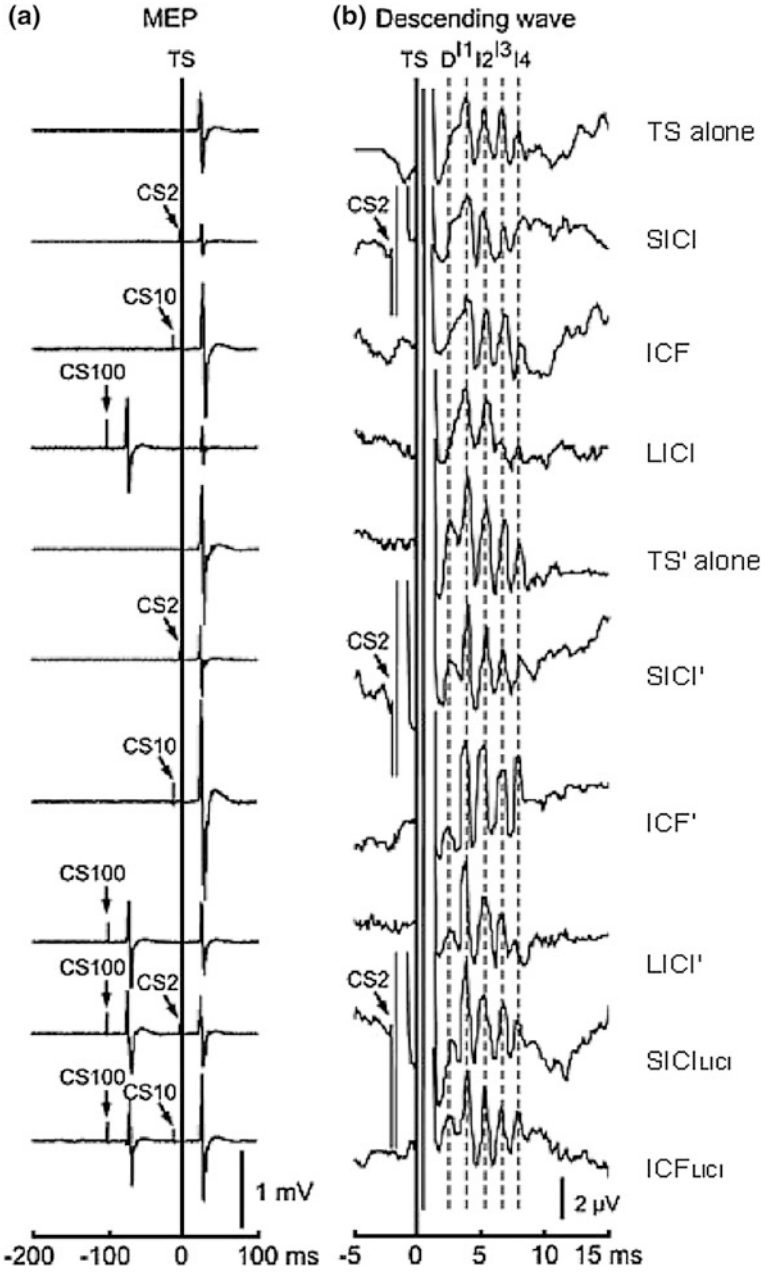
◀(Civardi et al. 2001). Studies using neuronavigation techniques identified different effects of CS applied to dorsal and ventral premotor cortices. CS at 80 % active motor threshold delivered to ventral premotor cortex facilitated the ipsilateral M1 at ISI of 4 or 6 ms, while the CS at 90 % resting motor threshold intensity suppressed M1 excitability at the same ISIs. On the other hand, CS delivered to dorsal premotor cortex at three different sites with similar stimulus parameters produced inconsistent effects on the M1 excitability, varying from inhibition to facilitation (Baumer et al. 2009). Facilitatory inputs from posterior parietal cortex to the ipsilateral M1 have been demonstrated with CS applied to caudal part of the inferior parietal sulcus at ISIs of 4 and 15 ms. Interestingly, facilitation only occurs with very specific stimulus parameters: the CS must induce posterior–anterior directed current at an intensity of 90 % resting motor threshold (Koch et al. 2007).

3.4 Interactions Between Intracortical Circuits

The intracortical circuits described above not only modulate motor cortical excitability, they are highly interconnected with each other. Interactions between these intracortical circuits can be studied with a triple-pulse TMS paradigm (Ni et al. 2011c).

3.4.1 Interaction Between SICI and LICI

The interaction between two intracortical circuits can be determined indirectly by comparing the effects of one circuit in the presence of the other to the effects of one circuit alone. Figure 3.4a shows MEPs recorded from one subject in whom the interaction between SICI and LICI was tested. The MEP amplitudes generated by TS alone and by LICI′ with higher TS intensity (TS′) were matched. This ensures similar corticospinal activity for testing SICI alone and SICI in the presence of LICI ($SICI_{LICI}$). Paired-pulse TMS with subthreshold CS2 (testing SICI, ISI between CS and TS 2 ms) inhibits the test MEP, while no further inhibition is found for SICI in the triple-pulse trial when LICI is present. These findings suggest that SICI is reduced in the presence of LICI (Sanger et al. 2001; Ni et al. 2011b). On the other hand, ICF is not significantly affected by LICI as determined by similar ICF_{LICI} (ICF in the presence of LICI) and ICF alone (Fig. 3.4a). TS' with increased intensities are used in this triple-pulse TMS paradigm to compensate for the decreased test MEP size in the presence of LICI. However, it has been argued that the adjustment in TS intensity may not be sufficient to compensate for the reduction of corticospinal activity because both SICI and LICI selectively target late I-waves (Nakamura et al. 1997; Di Lazzaro et al. 1998b, 2002), and the composition of I-waves may be different for TS alone and TS′ in the presence of LICI, even though MEP amplitude has been matched for the two experimental conditions with adjusted TS intensity.



In particular, test MEP for testing SICI alone in a paired-pulse paradigm (TS alone) may consist of more late I-waves and less early I-waves than test MEP for testing SICI in the presence of LICI in a triple-pulse paradigm (LICI′). Recordings of

◀**Fig. 3.4** Interaction between short-interval intracortical inhibition and long-interval intracortical inhibition. Up to three stimuli were employed in different experimental conditions. TS (marked with *vertical line*) was delivered in each trial. The time for delivery of the TS was defined as time 0. CS are named CS2, CS10, and CS100 according to the interstimulus interval between CS and TS. They are marked with arrows. **a** MEP recordings from −200 to 100 ms. **b** Descending wave recordings from 5 to 15 ms. Dash lines indicate the peaks of D-wave and I1–I4 waves. SICI represents trial in which TS was conditioned by a subthreshold CS2. ICF represents trial in which TS was conditioned by a subthreshold CS10. LICI represents trial in which TS was conditioned by a suprathreshold CS100. TS′ alone with higher intensity produced larger MEP and descending waves. SICI′, ICF′, and LICI′ represent trials of SICI, ICF, and LICI with TS′. MEP amplitudes for LICI′ and TS alone were matched to ∼1 mV. $SICI_{LICI}$ and ICF_{LICI} represent trials of SICI and ICF conditioned by LICI. TS alone generated MEP of ∼1 mV and produces I1-I4 waves. Note that late I-waves (I3, I4) were suppressed but the I1-wave was not affected by SICI and LICI. Neither MEP nor the descending wave was further inhibited in $SICI_{LICI}$ compared to LICI′. *CS* conditioning stimulus, *D-wave* direct wave, *I-wave* indirect wave, *ICF* intracortical facilitation, *ISI* interstimulus interval, *LICI* long-interval intracortical inhibition, *MEP* motor evoked potential, *SICI* short-interval intracortical inhibition, *and TS* test stimulus. Modified from Ni et al. (2011b)

descending corticospinal waves from epidural electrodes were used to address this important issue. Figure 3.4b shows that increasing the TS intensity was sufficient to compensate for the reduction of both MEP amplitude and late I-waves induced by LICI. The results confirmed that the inhibition of SICI by LICI cannot be explained by changes in I-wave content induced by LICI (Ni et al. 2011b). The time courses of the inhibitory effects of LICI on MEP and SICI are different (Chu et al. 2008; Cash et al. 2010). This is consistent with the suggestion that MEP inhibition is due to postsynaptic inhibition, whereas inhibition of SICI is due to presynaptic inhibition. Another important observation supporting this suggestion is that weak LICI that does not produce MEP inhibition also inhibits SICI (Sanger et al. 2001), indicating that the inhibitory effects of LICI onto the corticospinal neurons and SICI mediating neurons have different thresholds. With these experimental observations, it could be inferred that the inhibitory effects of LICI onto the corticospinal neurons and SICI mediating neurons are likely generated at different synaptic terminals. Since pharmacological studies have suggested that SICI is mediated by $GABA_A$ receptors (Ziemann et al. 1996a) while LICI is mediated by $GABA_B$ receptors (Siebner et al. 1998; Werhahn et al. 1999) and animal studies have demonstrated reduction of GABA release caused by presynaptic $GABA_B$ mediated inhibition in both the hippocampus (Pitler and Alger 1994) and the neocortex (Deisz 1999), the inhibitory interaction between LICI and SICI may be explained by presynaptic inhibition of GABAergic interneurons by LICI leading to reduction of GABA release that mediates SICI. This possible mechanism is further supported by a pharmacological study (Müller-Dahlhaus et al. 2008). Baclofen, a $GABA_B$ receptor agonist, increases LICI. To test the effect of baclofen on the interaction between SICI and LICI in a triple-pulse paradigm, both the intensities of the CS100 (for activating LICI, ISI between CS, and TS 100 ms) and TS were adjusted to match the degree of LICI after the drug intake to the baseline LICI. With this adjustment, it was found that baclofen had no effect on the interaction between SICI and LICI as the degree of decreased SICI in the presence of LICI was similar before and after the drug intake. This

finding is consistent with the conclusion that LICI suppresses SICI by presynaptic mediated inhibition, because adjustment in stimulus intensities after drug intake restored the activity of $GABA_B$ receptors both at the postsynaptic and presynaptic terminals which generated similar inhibitory effects before and after baclofen for both LICI and SICI in the presence of LICI (Müller-Dahlhaus et al. 2008).

The SP recorded during voluntary contraction is also mediated by $GABA_B$ receptors (Siebner et al. 1998; Werhahn et al. 1999). The interactions between SICI and LICI in active muscles have been investigated by testing of SICI during the SP. Decreased SICI during the SP has been demonstrated using a similar experimental protocol as that used for testing SICI in the presence of LICI at rest state. SICI at both ISIs of 1 and 2.5 ms was suppressed during the SP at 80, 110, and 140 ms after the delivery of the TMS pulse for generating the SP. In addition, SICI returns back to baseline after the recovery of background EMG (Ni et al. 2007). On the contrary, ICF during the SP was increased compared to ICF alone. This effect is different from ICF in the presence of LICI at rest (no interaction between ICF and LICI at rest, cf. Fig. 3.4). It has been proposed that intracortical circuits such as ICF are inhibited by voluntary drive (Ridding et al. 1995; Hanajima et al. 2002). Since voluntary drive is inhibited during the SP (Tergau et al. 1999), the increased ICF during the SP may be due to reduction of voluntary drive. Taken together, $GABA_B$ receptors mediated presynaptic inhibition is the most likely mechanism underlying the reduction of SICI in the presence of LICI with target muscle either at rest and active. ICF may be increased by LICI during voluntary contraction.

3.4.2 Interaction Between SICI and SICF

Wagle-Shukla et al. (2009) tested the interaction between SICI and SICF by applying a subthreshold CS3 (for activating SICI, ISI of 3 ms) followed by a suprathreshold TS and a second CS (for activating SICF, ISIs of 1.5, 2.9, 4.5 ms) at resting motor threshold intensity. The results showed that SICF was increased by SICI at the second (ISI 2.9 ms) and third peaks (ISI 4.5 ms) of SICF. SICF is produced by summation of inputs onto the same corticospinal neurons from different I-wave generating neurons activated by the TS and the second CS. In addition to the activation of the corticospinal neurons, it was suggested that the TS also activates a group of inhibitory interneurons which are responsible for the periodic discharge of corticospinal neurons. The finding may be explained if SICI (activated by CS3) inhibited both the corticospinal neurons and this group of inhibitory interneurons. The former led to SICI. The latter led to a disinhibitory effect in the triple-pulse paradigm manifested as increased SICF in the presence of SICI. In contrast, a subsequent study used an intensity of active motor threshold for CS3 and 1.4 times active motor threshold for the second CS found different results with suppression of SICF at the second peak and no change of SICF at the third peak in the presence of SICI (Shirota et al. 2010). With the relatively higher

intensity of the second CS (1.4 active motor threshold) that was used in this study, SICF may be saturated such that additional facilitation of SICF induced by SICI could not be detected. On the other hand, SICI decreased the excitability of corticospinal neurons and reduced the number of corticospinal neurons that could be activated by SICF. Therefore, the interaction between SICI and SICF may be complex and may depend on the strength of SICF being tested.

3.4.3 Interaction Between IHI and Intracortical Circuits Within M1

IHI is produced by transcallosal output from one hemisphere to the contralateral M1 (Ferbert et al. 1992a; Wahl et al. 2007). Similar to the corticospinal output, the transcallosal output from M1 is also mediated by pyramidal cells and is modulated by local intracortical circuits in the originating hemisphere (Somogyi et al. 1998). The modulation of local intracortical circuits on IHI in the originating hemisphere has been studied with triple-pulse TMS paradigm. The results suggest that SICI and LICI suppress SIHI, LIHI, and corticospinal output to a similar extent. In contrast, ICF increases corticospinal output without affecting SIHI or LIHI (Lee et al. 2007). This finding suggests that the neural circuits mediating corticospinal output and transcallosal output are different.

In the target hemisphere for IHI, inputs from the contralateral M1 also modulate local intracortical circuits in the M1. SIHI was found to reduce SICI. Since the reduction of SICI in the presence of SIHI correlates with the strength of SIHI but not with the strength of SICI itself, a suppressive effect of SIHI on SICI is considered likely. In contrast, ICF was not changed by SIHI. In addition, SIHI and LICI show a bidirectional inhibitory interaction with each other. This is demonstrated as reduced LICI in the presence of SIHI (Daskalakis et al. 2002; Müller-Dahlhaus et al. 2008) and reduced SIHI in the presence of LICI (Lee et al. 2007). SIHI and LICI may share some neural elements, although the pathways mediating these two intracortcial circuits are likely different (Irlbacher et al. 2007; Müller-Dahlhaus et al. 2008). The suppressed SICI in the presence of SIHI may be explained by SIHI activating local inhibitory circuits within the target M1 which partly overlap with those mediating LICI. Therefore, SICI may be inhibited by SIHI through presynaptic inhibition, similar to the decreased SICI in the presence of LICI. On the other hand, LIHI has little effect on SICI and ICF although there is a suppressive interaction between LIHI and LICI. These results suggest that LIHI also shares some common pathways with LICI. However, LIHI and SIHI are mediated by distinct pathways because the effects of SIHI and LIHI on SICI are different (Udupa et al. 2010).

3.4.4 *Sensory Afferent Inputs Affect Intracortical Circuits Within M1*

Local intracortical circuits are modulated by sensory afferent input. This interaction may be investigated by examining how a peripheral input such as electrical nerve stimulation (for eliciting SAI or LAI) changes local intracortical circuits. SAI generated by sensory afferent interacts with local intracortical circuits within the M1. Under slight voluntary contraction, SAI and SICI showed inhibitory interactions. The reduction of inhibition when the two circuits were activated together correlated with the strength of SICI but not with the strength of SAI. Since GABAergic neurotransmission is involved in both SICI and SAI, these findings raised the possibility that the synapses from SICI mediating neurons to the corticospinal neurons are located closer to the axon initial segment than those from the SAI mediating neurons. Such connectivity suggests a more powerful modulation of corticospinal neurons by SICI than SAI (Alle et al. 2009). In addition, LICI, which is mediated by $GABA_B$ receptors, was also reduced in the presence of SAI (Udupa et al. 2009). The effects of LAI and LICI were decreased when they were applied together. Since the reduction in inhibition was strongly correlated with the strength of LAI but not the strength of LICI, it is likely that LAI inhibits LICI. On the other hand, SICI and ICF remain unchanged in the presence of LAI, suggesting that LAI, SICI, and ICF are mediated by distinct pathways and their interactions are additive (Sailer et al. 2002).

3.4.5 *Effects of Cerebellum Projection on Intracortical Circuits Within M1*

Inputs from the contralateral cerebellar hemisphere modulate local intracortical circuits in the M1. SICI decreased and ICF increased in the presence of conditioning CBI, but the increase in ICF may be mediated through reduction in SICI. CBI and LICI inhibited each other, but the decreased inhibition did not correlate with the strength of either CBI or LICI (Daskalakis et al. 2004).

3.5 Conclusions and Future Studies

TMS studies with paired- and triple-pulse paradigms have greatly contributed to current knowledge of the functional organization of the complex motor cortical network. Figure 3.5 shows a model of the connectivity of individual intracortical circuits with the corticospinal neurons and the interactions among these circuits based on the current knowledge. The common excitatory interneurons (likely the late I-wave generating neurons) receive inputs from inhibitory interneurons which

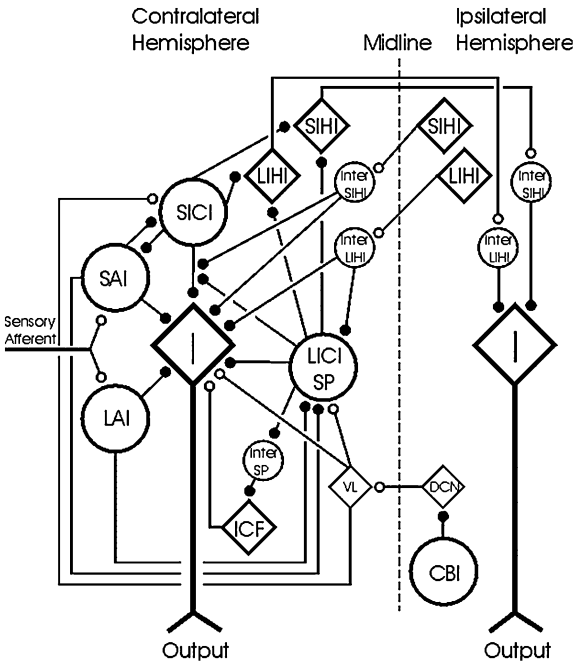


Fig. 3.5 Network model of intracortical circuits. The model is developed based on the known interactions among intracortical circuits. The *dotted line* represents the midline separating the hemispheres contralateral (*left*) and ipsilateral (*right*) to the target muscle. The *labeled circles* represent inhibitory interneurons and the rhombuses represent facilitatory interneurons. The *small filled circles* show inhibitory interactions and the *small open circles* show facilitatory interactions. The "common" facilitatory interneurons (*large rhombuses* labeled with I) receive inhibitory and facilitatory inputs from the intracortical circuits within and outside primary motor cortex, and project to corticospinal neurons which produce the output to the spinal motoneurons. In addition, these intracortical circuits have interactions with each other. *CBI* cerebellar inhibition, *DCN* deep cerebellar nuclei, *ICF* intracortical facilitation, *LAI* long latency afferent inhibition, *LICI* long-interval intracortical inhibition, *LIHI* long-interval interhemispheric inhibition, *SAI* short-latency afferent inhibition, *SICI* short-interval intracortical inhibition, *SIHI* short-interval interhemispheric inhibition, *SP* silent period, *and VL* ventral lateral thalamus. Modified from Ni et al. (2011c)

mediate SICI, LICI, SP, SAI and LAI, and from excitatory interneurons which mediate ICF. SAI and LAI mediating neurons are activated by sensory afferent inputs. The common interneurons also receive CBI mediated by inhibitory Purkinje cells from the contralateral cerebellar hemisphere that projects to the cortex via a disynaptic pathway through relays in the deep cerebellar nuclei and in the ventral lateral thalamus. SIHI and LIHI are mediated by excitatory projections through the motor corpus callosum, which synapse on local inhibitory interneurons in the opposite hemisphere. LICI and SP mediating neurons inhibit SICI mediating neurons through GABAB receptor mediated presynaptic inhibition. SAI, SIHI, and CBI mediating neurons also have inhibitory effect on SICI mediating neurons. In

addition, there may be bilateral inhibitory interaction between SAI and SICI mediating neurons. LICI mediating neurons are inhibited by SAI, LAI, CBI, and LIHI mediating neurons. SICI and LICI mediating neurons inhibit SIHI and LIHI, affecting the output to the contralateral hemisphere. On the other hand, ICF mediating neurons are facilitated by SP mediating neurons through disinhibition of inhibitory interneurons.

Although TMS studies have provided insight into the organization of motor cortical physiology, further studies need to address the functional significance of the proposed model and how it changes in behavior. Moreover, the clinical relevance of this functional network needs to be examined in neurological and psychiatric diseases, and in settings of cortical plasticity.

References

Alle H, Heidegger T, Krivanekova L, Ziemann U (2009) Interactions between short-interval intracortical inhibition and short-latency afferent inhibition in human motor cortex. J Physiol 587:5163–5176

Baumer T, Bock F, Koch G et al (2006) Magnetic stimulation of human premotor or motor cortex produces interhemispheric facilitation through distinct pathways. J Physiol 572:857–868

Baumer T, Schippling S, Kroeger J et al (2009) Inhibitory and facilitatory connectivity from ventral premotor to primary motor cortex in healthy humans at rest–a bifocal TMS study. Clin Neurophysiol 120:1724–1731

Butefisch CM, Netz J, Wessling M, Seitz RJ, Homberg V (2003) Remote changes in cortical excitability after stroke. Brain 126:470–481

Cash RF, Ziemann U, Murray K, Thickbroom GW (2010) Late cortical disinhibition in human motor cortex: a triple-pulse transcranial magnetic stimulation study. J Neurophysiol 103: 511–518

Chen R, Garg R (2000) Facilitatory I wave interaction in proximal arm and lower limb muscle representations of the human motor cortex. J Neurophysiol 83:1426–1434

Chen R, Tam A, Bütefisch C et al (1998) Intracortical inhibition and facilitation in different representations of the human motor cortex. J Neurophysiol 80:2870–2881

Chen R, Corwell B, Hallett M (1999) Modulation of motor cortex excitability by median nerve and digit stimulation. Exp Brain Res 129:77–86

Chen R, Yung D, Li J-Y (2003) Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. J Neurophysiol 89:1256–1264

Chen R, Cros D, Curra A et al (2008) The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 119:504–532

Chu J, Gunraj C, Chen R (2008) Possible differences between the time courses of presynaptic and postsynaptic GABAB mediated inhibition in the human motor cortex. Exp Brain Res 184:571–577

Civardi C, Cantello R, Asselman P, Rothwell JC (2001) Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. Neuroimage 14:1444–1453

Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R (2002) The mechanisms of interhemispheric inhibition in the human motor cortex. J Physiol 543:317–326

Daskalakis ZJ, Paradiso GO, Christensen BK, Fitzgerald PB, Gunraj C, Chen R (2004) Exploring the connectivity between the cerebellum and motor cortex in humans. J Physiol 557:689–700

Day BL, Dressler D, Maertens de Noordhout A et al (1989) Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. J Physiol 412:449–473
Deisz RA (1999) The GABA(B) receptor antagonist CGP 55845A reduces presynaptic GABA(B) actions in neocortical neurons of the rat in vitro. Neuroscience 93:1241–1249
Di Lazzaro V, Oliviero A, Profice P et al (1998a) Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. Electroencephalogr Clin Neurophysiol 109:397–401
Di Lazzaro V, Restuccia D, Oliviero A et al (1998b) Magnetic transcranial stimulation at intensities below active motor threshold activates inhibitory circuits. Exp Brain Res 119: 265–268
Di Lazzaro V, Rothwell JC, Oliviero A et al (1999) Intracortical origin of the short latency facilitation produced by pairs of threshold magnetic stimuli applied to human motor cortex. Exp Brain Res 129:494–499
Di Lazzaro V, Oliviero A, Profice P et al (2000) Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex. Exp Brain Res 135:455–461
Di Lazzaro V, Oliviero A, Saturno E et al (2001) The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. Exp Brain Res 138:268–273
Di Lazzaro V, Oliviero A, Mazzone P et al (2002) Direct demonstration of long latency cortico-cortical inhibition in normal subjects and in a patient with vascular parkinsonism. Clin Neurophysiol 113:1673–1679
Di Lazzaro V, Oliviero A, Pilato F et al (2004) The physiological basis of transcranial motor cortex stimulation in conscious humans. Clin Neurophysiol 115:255–266
Di Lazzaro V, Pilato F, Dileone M, Tonali PA, Ziemann U (2005) Dissociated effects of diazepam and lorazepam on short-latency afferent inhibition. J Physiol 569:315–323
Di Lazzaro V, Pilato F, Oliviero A et al (2006) Origin of facilitation of motor-evoked potentials after paired magnetic stimulation: direct recording of epidural activity in conscious humans. J Neurophysiol 96:1765–1771
Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992a) Interhemispheric inhibition of the human motor cortex. J Physiol 453:525–546
Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992b) Interhemispheric inhibition of the human motor cortex. J Physiol (Lond) 453:525–546
Fisher J, Nakamura Y, Bestmann S, Rothwell C, Bostock H (2002) Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking. Exp Brain Res 143:240–248
Fuhr P, Agostino R, Hallett M (1991) Spinal motor neuron excitability during the silent period after cortical stimulation. Electroencephalogr Clin Neurophysiol 81:257–262
Hallett M (2007) Transcranial magnetic stimulation: a primer. Neuron 55:187–199
Hanajima R, Ugawa Y, Terao Y et al (1998) Paired-pulse magnetic stimulation of the human motor cortex: differences among I waves. J Physiol 509:607–618
Hanajima R, Ugawa Y, Machii K et al (2001) Interhemispheric facilitation of the hand motor area in humans. J Physiol 531:849–859
Hanajima R, Ugawa Y, Terao Y et al (2002) Mechanisms of intracortical I-wave facilitation elicited with paired- pulse magnetic stimulation in humans. J Physiol 538:253–261
Ilic TV, Meintzschel F, Cleff U, Ruge D, Kessler KR, Ziemann U (2002) Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. J Physiol 545:153–167
Inghilleri M, Berardelli A, Cruccu G, Manfredi M (1993) Silent period evoked by transcranial stimulation of the human motor cortex and cervicomedullary junction. J Physiol 466:521–534
Irlbacher K, Brocke J, Mechow JV, Brandt SA (2007) Effects of GABA(A) and GABA(B) agonists on interhemispheric inhibition in man. Clin Neurophysiol 118:308–316
Koch G, Fernandez DO, Cheeran B et al (2007) Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. J Neurosci 27:6815–6822

Kujirai T, Caramia MD, Rothwell JC et al (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501–519
Lee H, Gunraj C, Chen R (2007) The effects of inhibitory and facilitatory intracortical circuits on interhemispheric inhibition in the human motor cortex. J Physiol 580:1021–1032
McDonnell MN, Orekhov Y, Ziemann U (2006) The role of GABA(B) receptors in intracortical inhibition in the human motor cortex. Exp Brain Res 173:86–93
Müller-Dahlhaus F, Liu Y, Ziemann U (2008) Inhibitory circuits and the nature of their interactions in the human motor cortex a pharmacological TMS study. J Physiol 586:495–514
Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H (1997) Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. J Physiol 498:817–823
Ni Z, Gunraj C, Chen R (2007) Short interval intracortical inhibition and facilitation during the silent period in human. J Physiol 583:971–982
Ni Z, Gunraj C, Nelson AJ et al (2009) Two phases of interhemispheric inhibition between motor related cortical areas and the primary motor cortex in human. Cereb Cortex 19:1654–1665
Ni Z, Charab S, Gunraj C et al (2011a) Transcranial magnetic stimulation in different current directions activates separate cortical circuits. J Neurophysiol 105:749–756
Ni Z, Gunraj C, Wagle-Shukla A et al (2011b) Direct demonstration of inhibitory interactions between long interval intracortical inhibition and short interval intracortical inhibition. J Physiol 589:2955–2962
Ni Z, Müller-Dahlhaus F, Chen R, Ziemann U (2011c) Triple-pulse TMS to study interactions between neural circuits in human cortex. Brain Stimul 4:281–293
Patton HD, Amassian VE (1954) Single and multiple unit analysis of the cortical stage of pyramdial tract activation. J Neurophysiol 17:345–363
Peurala SH, Muller-Dahlhaus JF, Arai N, Ziemann U (2008) Interference of short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF). Clin Neurophysiol 119:2291–2297
Pinto AD, Chen R (2001) Suppression of the motor cortex by magnetic stimulation of the cerebellum. Exp Brain Res 140:505–510
Pitler TA, Alger BE (1994) Differences between presynaptic and postsynaptic GABAB mechanisms in rat hippocampal pyramidal cells. J Neurophysiol 72:2317–2327
Ridding MC, Taylor JL, Rothwell JC (1995) The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. J Physiol 487:541–548
Roshan L, Paradiso GO, Chen R (2003) Two phases of short-interval intracortical inhibition. Exp Brain Res 151:330–337
Sailer A, Molnar GF, Cunic DI, Chen R (2002) Effects of peripheral sensory input on cortical inhibition in humans. J Physiol 544:617–629
Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I (1997) Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. Exp Brain Res 113:24–32
Sanger TD, Garg RR, Chen R (2001) Interactions between two different inhibitory systems in the human motor cortex. J Physiol 530:307–317
Shirota Y, Hamada M, Terao Y et al (2010) Influence of short-interval intracortical inhibition on short-interval intracortical facilitation in human primary motor cortex. J Neurophysiol 104:1382–1391
Siebner HR, Dressnandt J, Auer C, Conrad B (1998) Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. Muscle Nerve 21:1209–1212
Somogyi P, Tamas G, Lujan R, Buhl EH (1998) Salient features of synaptic organisation in the cerebral cortex. Brain Res Brain Res Rev 26:113–135
Tergau F, Wanschura V, Canelo M et al (1999) Complete suppression of voluntary motor drive during the silent period after transcranial magnetic stimulation. Exp Brain Res 124:447–454
Tokimura H, Ridding MC, Tokimura Y, Amassian VE, Rothwell JC (1996) Short latency facilitation between pairs of threshold magnetic stimuli applied to human motor cortex. Electroencephalogr Clin Neurophysiol 103:263–272

Tokimura H, Di Lazzaro V, Tokimura Y et al (2000) Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol 523:503–513

Udupa K, Ni Z, Gunraj C, Chen R (2009) Interactions between short latency afferent inhibition and long interval intracortical inhibition. Exp Brain Res 199:177–183

Udupa K, Ni Z, Gunraj C, Chen R (2010) Effect of long interval interhemispheric inhibition on intracortical inhibitory and facilitatory circuits. J Physiol 588:2633–2641

Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I (1995) Magnetic stimulation over the cerebellum in humans. Ann Neurol 37:703–713

Valls-Solé J, Pascual-Leone A, Wassermann EM, Hallett M (1992) Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr Clin Neurophysiol 85:355–364

Wagle-Shukla A, Ni Z, Gunraj CA, Bahl N, Chen R (2009) Effects of short interval intracortical inhibition and intracortical facilitation on short interval intracortical facilitation in human primary motor cortex. J Physiol 587:5665–5678

Wahl M, Lauterbach-Soon B, Hattingen E et al (2007) Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. J Neurosci 27: 12132–12138

Wassermann EM, Samii A, Mercuri B et al (1996) Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscle. Exp Brain Res 109:158–163

Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J (1999) Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J Physiol 517: 591–597

Ziemann U (2004) TMS drug. Clin Neurophysiol 115:1717–1729

Ziemann U, Rothwell JC (2000) I-waves in motor cortex. J Clin Neurophysiol 17:397–405

Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W (1996a) Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 40: 367–378

Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W (1996b) The effect of lorazepam on the motor cortical excitability in man. Exp Brain Res 109:127–135

Ziemann U, Rothwell JC, Ridding MC (1996c) Interaction between intracortical inhibition and facilitation in human motor cortex. J Physiol 496:873–881

Ziemann U, Tergau F, Wassermann EM, Wischer S, Hildebrandt J, Paulus W (1998a) Demonstration of facilitatory I wave interaction in the human motor cortex by paired transcranial magnetic stimulation. J Physiol 511:181–190

Ziemann U, Tergau F, Wischer S, Hildebrandt J, Paulus W (1998b) Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. Electroencephalogr Clin Neurophysiol 109:321–330

Chapter 4
Effects of Cortical Stimulation on Cortical Functional Connectivity: Imaging Studies

Steffen Angstmann and Hartwig Roman Siebner

Abstract Functional magnetic resonance imaging (fMRI) and other functional brain mapping techniques have emerged as valuable means of studying the dynamic interactions within and between functional brain systems. Functional interactions can be studied while participants are at rest (i.e., so-called resting-state connectivity) or while they perform an experimental task. Functional mapping of brain connectivity has provided important insights into the functional neuroanatomy of the human brain. Connectivity analyses assess temporospatial correlations of distributed brain activity. The correlative nature of brain mapping renders it difficult to draw causal conclusions about the information flow within interconnected brain areas. Here, the interventional nature of transcranial magnetic stimulation (TMS) adds another dimension to the study of brain connectivity by inducing neural activity in a cortical region. Depending on the intensity of stimulation and the functional state of the network, the regional activity induced by focal TMS can transsynaptically spread to other elements (regions) in the network via the existing cortico–cortical and cortico-subcortical connections. This virtue of TMS opens up a range of possibilities to interfere with the distributed activity in functional networks and to trace causal interactions. This chapter highlights how TMS can be combined with neuroimaging techniques to unravel causal interactions in the human brain both in healthy individuals and patients with brain diseases. This chapter covers conceptual and methodical aspects and illustrates the potential and problems associated with combining TMS and neuroimaging simultaneously (i.e., online TMS) or sequentially (i.e., offline TMS).

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4.1 Brain Connectivity

4.1.1 Conceptual Issues

The human nervous system expresses network properties at every organisational level. This applies to regional microcircuits within a single brain region as well as to macrocircuits that connect multiple regions in the brain forming functional systems. To understand how neurons and neural networks process information is a fundamental question in neuroscience. The integration of information is conveyed by structural links such as synapses or fibre pathways which constrain the information flow among distinct functional units of functional networks. Depending on the organisational level, the functional units correspond to individual neurons, neuronal populations or anatomically segregated brain regions. At the systems level, the brain contains a large set of functional networks which subserve distinct brain functions and express highly dynamic patterns of functional interactions within and among networks (Sporns et al. 2004; Bullmore and Sporns 2009). These network dynamics are not static but are continuously shaped by experience and learning depending on both environmental and genetic factors.

Recent years have witnessed major efforts to unravel the brain's structural and functional *connectome*, that is to map and understand the organisation of neural interactions within the entire human brain (Sporns et al. 2005). Modern network approaches have started to reveal insights into the fundamental principles of the brain network architecture (Hagmann et al. 2010; Friston 2011). The focus on brain connectivity reflects a paradigm shift in neuroscience shifting the focus from one-to-one mappings (i.e., functional localisation) to studies of interrelations between distinct units of a network or among networks (i.e., functional integration). If we want to understand the functioning of a given brain network, it is not sufficient to know its elements, but one needs to understand its connectivity. We need to know how these elements are interconnected and how they interact with each other in a context-dependent fashion to support a specific brain function.

From a conceptual point of view, it is helpful to distinguish between three expressions of brain connectivity: structural connectivity (fibre pathways), functional connectivity (correlations) and effective connectivity (information flow) (Friston 1994) (Fig. 4.1). It should be mentioned that these different types of connectivity are not independent of each other; in fact, their interrelations constitute a major challenge for current neuroscience (Sporns et al. 2005; Damoiseaux and Greicius 2009; Greicius et al. 2009).

4.1.2 Structural Connectivity

Structural connectivity describes the anatomical connections that exist among the relevant elements of a brain network. Although structural connectivity refers to the

hard-wired neural tracts linking the brain network, structural connectivity is not static but subjected to plasticity like the other modes of connectivity. Indeed, dynamic changes occur at longer time scales especially during brain maturation (weeks to years), so that structural connectivity can be regarded to be relatively stable at shorter time scales (seconds to minutes). The strength of white matter tracts connecting two brain regions can be used as a metric to describe the strength of a cerebral connection (Sporns et al. 2005).

Recent advances in tractography based on diffusion-weighted magnetic resonance imaging (DWI) have considerably expanded the possibilities to non-invasively assess structural brain connectivity in the human brain (Johansen-Berg and Rushworth 2009). DWI techniques measure the regional diffusion of water molecules in each voxel. Due to the fact that molecules travel faster along a fibre than perpendicular to it, DWI provides information on the microstructure and fibre orientation of white matter tracts. However, the microstructural measures that can be derived from DWI are typically ambiguous in biological terms and provide no information on the directionality of a connection. DWI-based methods also have limited spatial resolution which precludes mapping connections at the level of single axons. Technically, it is still difficult to resolve multiple tracts in white matter regions with crossing fibres. Despite of these limitations, DWI has yielded important insights in the organisation of large-scale brain networks and the dynamics of microstructural properties of distinct tracts in the human brain (Johansen-Berg and Rushworth 2009; Hagmann et al. 2010).

Due to the relative stability of hard-wired structures and the slow time scale of their dynamic behaviour, DTI measures are usually not combined with an *experimental manipulation* of brain state (i.e. a task in the scanner). The focus rather lies on finding stable *behavioural traits* that can be linked to structural characteristics of white matter connectivity (Johansen-Berg 2010). However, a recent DWI study in healthy adult individuals found that training of a complex visuo-motor skill resulted in a sub-acute increase in regional fractional anisotropy, a measure of regional microstructure, in the white matter underlying the intraparietal sulcus. This finding suggests that some microstructural white matter properties can undergo relatively fast changes in response to changes in sensorimotor experience (Scholz et al. 2009).

4.1.3 Functional Connectivity

Functional connectivity describes the temporal coupling of regional neural activity among remote brain areas. It provides information on the amount of *shared changes in activity* among brain regions, regardless of assumptions about underlying pathways, structure or causality. Measures used to describe the strength of such a coupling are statistical by nature. Widely employed parameters are correlation and coherence but also other methods like regression analysis, principal component analysis (PCA) or multidimensional scaling are applicable (Hampson et al. 2012). It is important to recall that all metrics of functional connectivity

contain no information on the direction of information flow within the connectome or the pathways that mediate functional connectivity. This applies also to the numerous studies focusing on functional brain connectivity as revealed by resting-state fMRI (Gusnard and Raichle 2001).

Functional connectivity can be assessed during different "brain states". Functional activation studies can identify functional connectivity related to a specific *experimental task*. The derived functional connectivity can be correlated with behavioural measures and changes in task performance can be set in relation to changes in functional connectivity. Alternatively, it is possible to study functional brain connectivity while participants are at rest (i.e., without performing any task). This approach has been widely used in recent years. Resting-state functional magnetic resonance imaging (rs-fMRI) measures spontaneous low frequency (<0.1 Hz) fluctuations in the blood-oxygen-level dependent (BOLD) signal over 5–30 min (Biswal et al. 1995; Fox and Raichle 2007). These fluctuations are temporally correlated within functional brain networks, and thus provide an index of functional connectivity. The use of rs-fMRI has gained wide popularity as a means of studying functional brain organisation in health and disease (Deco et al. 2011). Rs-fMRI is particularly suited for functional connectivity studies in patients with functional deficits who are impaired at performing experimental tasks. The connectivity patterns revealed by rs-fMRI are not confounded by task performance as patients do not need to engage in a specific task. Resting-state functional connectivity can be studied with other imaging modalities as well, including rs-EEG, rs-MEG or rs-PET of regional metabolic rate of glucose or regional cerebral blood flow. One of the most extensively studied resting-state networks is the so-called *default mode network* (DMN) (Raichle et al. 2001; Raichle and Snyder 2007). This network is thought to be involved in spontaneous, self referential mental activity. Interestingly, resting-state activity reflects structural connectivity (Greicius et al. 2009; Honey et al. 2009).

When assessing functional connectivity, researchers can adopt different strategies to define which brain regions are included in the analysis. Brain regions can be defined beforehand (*a priori*). For instance, one may constrain connectivity analysis anatomically to a pre-defined set of regions of interest (ROIs). Alternatively, functional connectivity analysis may be entirely data driven based on the temporospatial features inherent in the data. A prominent example for a data-driven analytic approach is independent component analysis (ICA) but other unsupervised techniques are also available (Rogers et al. 2007; Hampson et al. 2012).

4.1.4 Effective Connectivity

Effective connectivity describes connectivity in brain networks in terms of directional and context dependent effects of one neural element on other elements (Buchel and Friston 1998; Pastor et al. 2000). This concept probably matches best

our intuitive notion of a causal influence as it makes a statement about the information flow between brain sites (Friston 1994). However, "real" causal interactions can only be inferred through systematic perturbations of the system.

An alternative criterion to infer causality is temporal dependence as revealed by time series analysis where a "cause" (i.e., causal neural activity in region A) consistently precedes an "outcome" (i.e., triggered neural activity in region B). Thus, causality assessed in the context of brain imaging and effective connectivity is a mathematical concept; it is derived from data patterns and model assumptions and must not be mixed up with causal conclusions drawn due to experimental manipulation.

Some techniques for extracting effective connectivity are "model-based" such as dynamic causal modelling (DCM). They require the specification of a model which may include structural parameters. DCM was originally developed for estimating the influence of an experimental manipulation on context-dependent information flow between brain regions (Friston et al. 2003). Therefore, the design of the experimental task may have important impact on the subsequent analysis and need to be fine tuned to enable an optimal use of DCM. A recent extension of DCM enables its application to resting-state fMRI data without relying on prior knowledge about experimental causes (Friston et al. 2011; Li et al. 2011). Other techniques are largely "model-free". For instance, effective connectivity can be inferred using time series analysis which provides measures such as Granger causality or transfer entropy. Here the basic assumption is that causes must precede effects in time. For DCM, Granger causality and a number of other network measures (Rubinov and Sporns 2010), toolboxes are available which allow for the application of these methods to fMRI and EEG/MEG data, many of them freely available open source.

The different analytical methods rely on different additional assumptions and statistical properties Friston (2009). DCM has built-in biophysical assumptions of how observed data were generated. It is more complicated to handle but might be more adequate for that very type of data as well. Granger causality has no such built-in biological model but relies on statistical dependencies of the data themselves and does not try to estimate hidden causes of how these were generated. The use of Granger causality to infer effective connectivity from functional magnetic resonance imaging (fMRI) data has been challenged recently, because of the inherent temporal variability of the regional neurovascular BOLD response. Its use to infer effective connectivity from fMRI data sets is currently subject of investigation (Roebroeck et al. 2005; Deshpande et al. 2010). Please see (Friston 2009) for a more elaborate comparison of DCM and Granger causality.

4.2 What can TMS Add to Functional Neuroimaging of Brain Connectivity?

When using a functional brain mapping technique to assess functional or effective connectivity, it is crucial to consider which neural process is mapped by the neuroimaging modality. This particularly applies to the nature of the signal

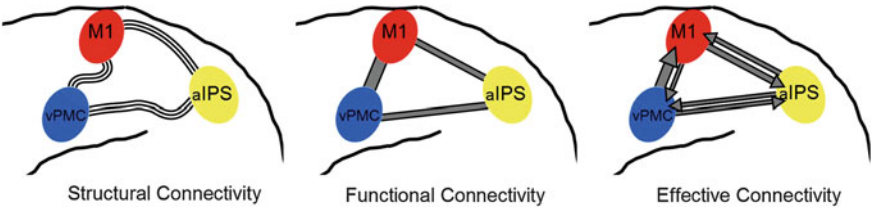

Fig. 4.1 Different types of connectivity between brain sites representing a simplified network involved in sensorimotor control of grasping: *Structural connectivity* refers to the anatomical connections between different brain areas that constitute important elements within the network. *Functional connectivity* reflects how strong the regional activity levels in the identified network components are correlated in time (i.e., temporo-spatial covariance). This temporo-spatial covariance pattern provides no information regarding directionality (*undirected edges*). *Effective connectivity* describes the influence one region exerts over another. This influence is represented by a weighted graph which comprises the brain regions as nodes and its effective connections as directed edges. *vPMC* ventral premotor cortex; *M1* primary motor hand area, *aIPS* anterior intraparietal sulcus

generator and its temporal characteristics. Non-invasive methods like EEG and MEG, which are acquired at the skull surface *directly* measure neural activity. They capture neural activity on the millisecond time scale, and thus offer high temporal resolution. Their spatial accuracy, however, is limited (centimetres) as many unknown parameters must be estimated when calculating the presumed source of activation. Other neuroimaging methods measure neural activity only *indirectly* by mapping changes in regional brain perfusion and blood oxygenation caused by regional changes in neural activity. Such mapping techniques based on neurovascular coupling show inverse characteristics in terms of temporal and spatial resolution relative to EEG or MEG; they offer high spatial (millimetres) but limited temporal resolution. The most widely employed neurovascular method is BOLD-sensitive fMRI (Ogawa et al. 1990). Due to the hemodynamic response function, the BOLD signal has a considerable (around 4 s) but ,nonetheless, stable delay with respect to the underlying neural activity. In contrast to positron emission tomography (PET) of regional cerebral blood flow or metabolic rate of glucose, BOLD sensitive fMRI does not involve exposure to radiation and offers superior spatial and temporal resolution. The latter allows for analysis of event-related activity and renders fMRI suitable for studies of functional and effective brain connectivity, at rest as well as during motor- and non-motor tasks.

Functional brain mapping techniques such as fMRI or PET have emerged as valuable means for studying the interactions within and among functional brain systems while participants are at rest or perform an experimental task. While such studies have provided important insights into the functional neuroanatomy of the human brain, their correlative nature renders it difficult to infer the causal role of the functional interactions among connected brain areas.

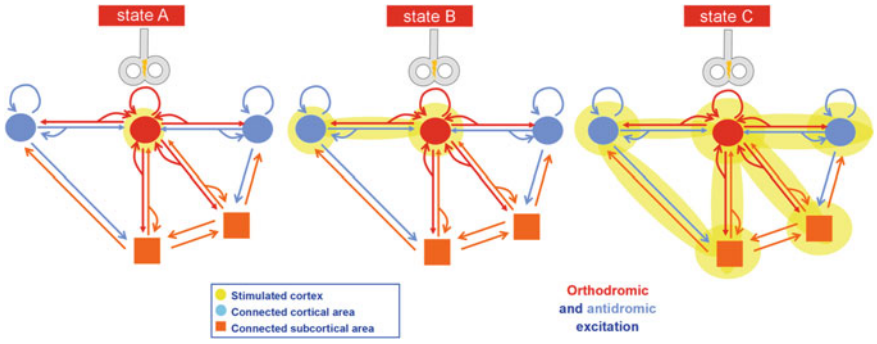

Fig. 4.2 "Focal" TMS can produce remote effects via transsynaptic spread of excitation throughout the brain network. The network effects of TMS hereby depend on a number of variables such as the excitability of the cortical target area, the intensity of stimulation and the timing of stimulation with respect to the intrinsic functional state of the stimulated cortex and its connections (state A-C)

4.2.1 Single-Site TMS During Neuroimaging ("Online" TMS)

Transcranial magnetic stimulation (TMS) adds a causal dimension to the study of brain connectivity, because TMS can be used to experimentally manipulate neural activity in a specific cortical region. When the intensity of TMS is sufficiently strong, a single TMS pulse elicits highly synchronised action potentials in the stimulated cortical area which interfere with the ongoing intrinsic neural activity. If the stimulated cortical region is critical to a specific function, the transient "lesion effect" of TMS may result in a behavioural impairment in tasks that rely on the perturbed brain function. By applying a single TMS pulse or a short train of high-frequency TMS during an experimental task, it is possible to characterise whether and when the stimulated cortex is relevant for a specific brain function (Walsh and Rushworth 1999; Pascual-Leone et al. 2000). This *"virtual lesion" approach* to induce a transient functional lesion is now firmly established as an interventional tool in cognitive neuroscience. The functional and behavioural effects of TMS are highly dependent of the "neural context" (i.e., the functional state of the stimulated cortex). In other words, the brain response to TMS depends on how excitable the cortical elements are at the time the stimulus is applied (Silvanto et al. 2007; Siebner et al. 2009b).

Depending on the intensity of stimulation and the functional state of the network, the regional activity induced by focal TMS may spread to other components in the network by inducing action potentials in cortico–cortical and cotico-subcortical connections (Fig. 4.2). The spread of excitation to remote connected area may use orthodromic conduction along efferent connections from the stimulated cortex to remote areas (Fig. 4.2). However, it is also possible that TMS additionally results in an antidromic spread of excitation by inducing action potentials in afferent projections (Fig. 4.2) that project from remote areas onto the stimulated cortex. This property of TMS opens up a range of possibilities to map causal

interactions in the human brain. In this context, "online" TMS during functional neuroimaging can trace how TMS-induced regional activity propagates through functional brain networks and hereby alters the temporo-spatial pattern of intrinsic brain activity in a context-dependent fashion (Siebner et al. 2009a).

4.2.2 Assessing Cortico–Cortical Connectivity with Dual-Site TMS

Dual-site transcranial magnetic stimulation (ds-TMS) simultaneously targets two connected cortical areas in a coordinated fashion, and therefore can be used to study specific cortico–cortical fibre tracts in the intact human cortex. The ds-TMS approach was first introduced by Ferbert et al. (1992) and consists of a supra-threshold test stimulus (TS) which is applied to the primary motor hand area ($M1_{HAND}$) and evokes a motor evoked potential (MEP) in a contralateral hand muscle.

A conditioning stimulus (CS) is delivered through a second coil over a remote brain area that is functionally connected with the $M1_{HAND}$. The TS over $M1_{HAND}$ is given either in isolation or after CS. The facilitatory or inhibitory effect of the CS on the MEP amplitude can be used to characterise the functional connectivity between the remote cortical area and the $M1_{HAND}$ area. This electrophysiological approach has been successfully used as a physiological approach to characterise inter-and intra-hemispheric functional connectivity between frontal areas and the $M1_{HAND}$ both at rest and during manual motor tasks (Mochizuki et al. 2004; Baumer et al. 2006; Boorman et al. 2007; Koch et al. 2007; O'Shea et al. 2007; Davare et al. 2008; Davare et al. 2010).

The ds-TMS approach has also been used to study the functional impact of dorsal premotor cortex (PMd) on $M1_{HAND}$ in the intact human brain. These studies have revealed facilitatory and inhibitory inter-hemispheric interactions between the PMd and contralateral $M1_{HAND}$ which critically depended on the timing, direction and intensity of the CS pulse as well as the motor state (Mochizuki et al. 2004; Baumer et al. 2006; O'Shea et al. 2007; O'Shea et al. 2007). In a recent study, a new paradigm has been introduced in which excitability of the left $M1_{HAND}$ was modulated by a CS over ipsilateral PMd given 2.8 or 4 ms after the TS (Groppa et al. 2011).

So far, ds-TMS has been limited to study the impact of inputs to the primary motor cortex using the MEP amplitude as functional read out. Here, ds-TMS during functional neuroimaging could extend the application of ds-TMS to probe cortico–cortical connectivity between non-motor brain regions, for instance, by using the regional neurovascular response as read out. Furthermore, DWI can be used to map the white matter microstructure of the cortico–cortical tracts that is assessed with ds-TMS and to relate relate inter-individual variations in functional and structural cortico–cortical connectivity (Boorman et al. 2007).

4.2.3 *Repetitive TMS to Induce Lasting Changes in Brain Connectivity ("Offline" TMS)*

By applying TMS in its "conditioning" mode, repetitive TMS (rTMS) can be used to promote short-term changes in effective brain connectivity (Siebner and Rothwell 2003). A multitude of new conditioning rTMS protocols has been introduced in the last decade which can be used to effectively shape regional excitability beyond the time of stimulation (Ziemann et al. 2008). Importantly, the conditioning effects of rTMS are not limited to the stimulated cortical area, but may induce more widespread functional reorganisation (Siebner et al. 2009a). This includes changes in weight of functional connectivity strength in the targeted brain network as well as changes in regional activity in connected brain areas.

The ability of TMS to trigger acute functional reorganisation is of particular relevance to connectivity studies in the human brain. Mapping the rTMS-induced changes in functional and effective brain connectivity with fMRI and other functional neuroimaging techniques offers valuable insights into the changeability of the functional architecture of brain networks. As for the acute "lesion effects" of online TMS, the conditioning (offline) effects of rTMS critically depend on the functional state of the targeted brain network.

4.3 Combining Transcranial Magnetic Stimulation and Neuroimaging

TMS and functional neuroimaging feature inherent strengths and weaknesses. Due to its limited depth penetration, only cortical areas close to the hemispheric surface can be directly targeted by TMS. Furthermore, the options to assess the effects of TMS on brain connectivity are mainly limited to the motor system, because TMS studies mainly rely on the measurement of TMS evoked motor responses. On the other hand, functional brain imaging offers whole-brain coverage and good spatial resolution. Temporal resolution is, however, limited and functional brain mapping alone cannot prove causality. The specific strengths and weaknesses of TMS and functional neuroimaging provide a strong motivation for combining TMS and fMRI to study brain connectivity. TMS can be used to effectively disrupt or shape functional interactions in the targeted brain network, while fMRI can readily map the functional impact of TMS on network connectivity. This opens up numerous interesting applications. For instance, functional brain imaging can be used to examine which changes in brain connectivity cause or prevent a TMS-evoked change in behaviour.

Several options exist how to combine TMS with MRI in order to study brain connectivity (Fig. 4.3). First, dual-site TMS can be used to study functional and effective connectivity in specific cortico–cortical pathways (Fig. 4.3a). These measures of functional cortico–cortical connectivity can be related to the

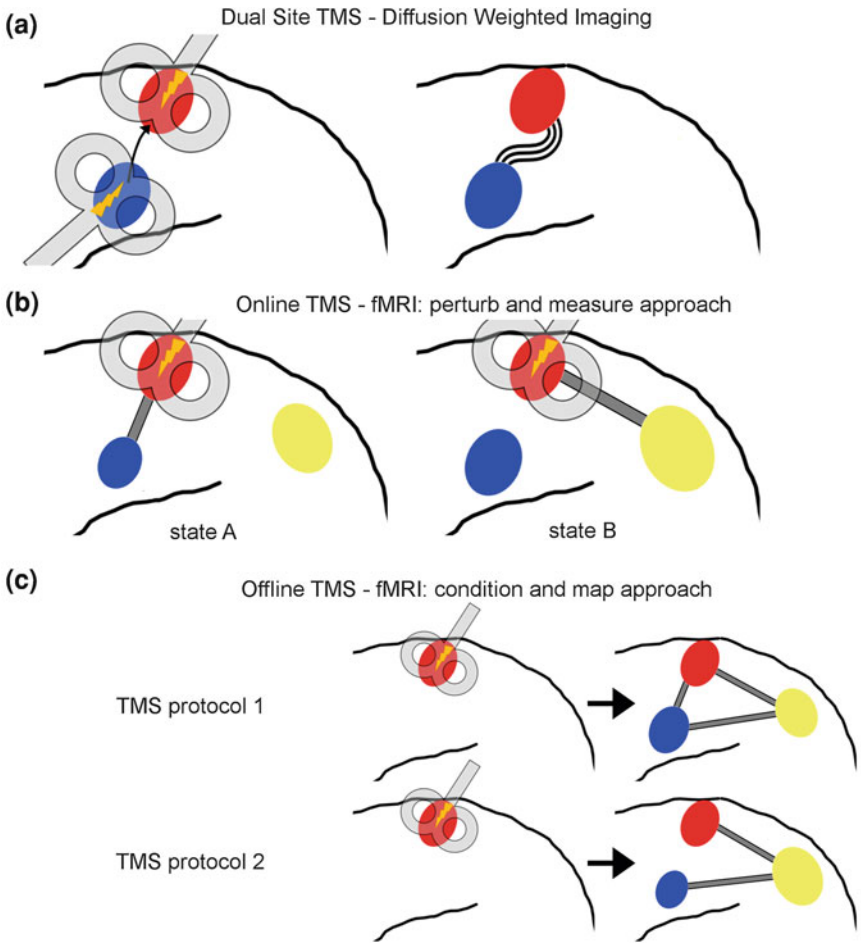

Fig. 4.3 The combined use of brain imaging and TMS. **a** Combination of DWI to assess white matter microstructure and dual-site TMS. **b** Online "perturb-and-measure" approach using interleaved TMS and fMRI. **c** Offline "condition and map" approach, applying a conditioning TMS protocol followed by fMRI. In two separate sessions stimulation is administered in a counterbalanced order (usually a real TMS condition versus a sham or control TMS condition)

microstructural properties in the corresponding cortico–cortical white matter tract as reflected by DWI. Second, TMS can be interleaved with fMRI to map the immediate alterations in functional and effective connectivity in response to focal TMS (Fig. 4.3b). Third, rTMS can be used to induce a reweighting of the distributed connectivity pattern in the targeted brain network. The rTMS-induced changes in connectivity strength can then be assessed with fMRI (Fig. 4.3c).

4.3.1 Transcranial Magnetic Stimulation and Diffusion-Weighted Imaging

Dual-site TMS can be used to probe the excitability of inputs from fronto-parietal areas to the $M1_{HAND}$ by measuring how a conditioning TMS pulse given over the remote cortical area modifies the MEP amplitude evoked by TMS of the $M1_{HAND}$ (see Sect. 4.2.3 for detailed description). The conditioning effects on MEP amplitude are subject to context-dependent changes reflecting changes in effective connectivity (Koch et al. 2006; 2008). Several studies have related the electrophysiological indices of cortico–cortical connectivity (as revealed by dual-site TMS) to microstructural properties of the cortico–cortical connection in healthy volunteers. These studies have used diffusion tensor magnetic resonance imaging (DTI) to assess the microstructure of the white matter. Two quantitative parameters of regional water diffusion can be derived from the measured effective diffusion tensor: mean diffusivity (MD) and fractional anisotropy (FA) as metrics of regional diffusion. MD reflects the overall magnitude of regional water diffusion regardless of the direction of diffusion, whereas FA provides an eccentricity measure of regional diffusion. In other words, FA reflects how much the regional diffusion of water molecules does preferentially occur along a specific direction in a given voxel. The diffusion tensor model also provides a measure for the magnitude of regional diffusion parallel and perpendicular to the major direction of the diffusion tensor.

In a seminal paper, Wahl et al. (2007) used DTI to investigate the microstructure of the corpus callosum and measured interhemispheric inhibition (IHI) between the $M1_{HAND}$ using dual-site TMS (Wahl et al. 2007). The microstructure of the corpus callosum as assessed by DTI correlated with the strength of IHI: the higher regional FA in the motor region of the corpus callosum, the stronger IHI was expressed in the participants. The linear relation between regional FA and the strength of IHI was somatotopically specific as it was only seen for the part of the corpus callosum containing the fibres that connect the two $M1_{HAND}$, but not for the adjacent callosal region linking the primary motor foot areas. Thus, the authors were able to show, that inter-individual variations of specific microstructural properties in the cortico–cortical tract that is presumably probed with dual-site TMS correlates with the functional connectivity as probed with dual-site TMS.

A subsequent study combined diffusion-tensor MRI and dual-site TMS to link regional subcortical FA with changes in effective cortico–cortical connectivity during an experimental task (Boorman et al. 2007). Participants performed a visually cued movement selection task, requiring alternative button presses with the left or right index finger depending on the visual instruction cue. The ds-TMS paradigm consisted of a CS over the PMd and a TS over contralateral $M1_{HAND}$. The increase in inter-hemispheric PMD-to-M1 connectivity during action selection correlated with higher FA values in localised regions of white matter interconnecting motor regions, including the PMd and M1.

Two recent studies examined the relationship between TMS measures of corticomotor excitability and microstructural measures of the corticospinal tract

(Kloppel et al. 2008; Hubers et al. 2011). Kloppel et al. applied single-site TMS to $M1_{HAND}$ to measure the cortical motor threshold (MT) which reflects the excitability of corticospinal neurons. Voxel-wise analysis revealed that the active and resting MT were negatively related to regional FA values in large parts of cerebral white matter, highlighting structural covariates of corticospinal connectivity and motor cortex excitability and indicating that a stronger directional organisation is associated with faster neuronal transduction. However, regions showing such correlations were generally found outside of the corticospinal tract which speaks against the notion that the MT reflects microstructural properties of the corticospinal tract, at least in the healthy brain. Hubers et al. (2011) used tract-based statistics to show correlations between regional FA and bilateral AMT as well as between regional FA and the intensity to evoke a motor-evoked potential of 1 mV in the left $M1_{HAND}$, but again these correlations were found in locations unlikely to contribute to motor pathways.

One might expect a stronger relation between the microstructure of the corticospinal tract (assessed with DWI) and the strength of functional connectivity in these pathways (as revealed by single-pulse TMS) during the maturation of the corticospinal tract or in pathological conditions resulting in a damage of corticospinal fibres. Indeed, patients with amyotrophic lateral sclerosis showed a decrease in FA in the corticospinal tract, even if they showed no clinical signs of upper motor neuron lesion (Sach et al. 2004). In these patients, single-pulse TMS revealed a negative linear relationship between central motor conduction time to the arm and leg and regional FA in the corresponding corticospinal tract fibres supplying the upper and lower extremities (Sach et al. 2004).

4.3.2 Online TMS During Functional Neuroimaging: "Perturb-and-Measure" Approach

Functional neuroimaging during TMS allows for mapping the acute spatiotemporal changes in brain activity and connectivity caused by TMS. Tomáš Paus coined the term "*perturb-and-measure*" approach with reference to the online lesion effects of TMS at the behavioural level (Paus 2005). When applying TMS during neuroimaging, one has to take into account that TMS always results in concurrent auditory and sensory brain stimulation which has multiple indirect effects on the observed brain activity pattern.

4.3.2.1 Online TMS During Positron Emission Tomography

Online TMS has been successfully applied during positron emission tomography (PET) (Fox et al. 1997; Paus et al. 1997, 1998; Siebner et al. 1998). The PET modality can be used to investigate the regional binding and metabolism of compounds that have been tagged with short-lived positron-emitting isotopes such

as carbon-11, oxygen-15 or fluorine-18. PET provides three-dimensional images of the tracer distribution in the brain and offers a range of possibilities to study functional brain connectivity. Depending on the radioactive tracers, PET can be used to map regional cerebral blood flow (rCBF) or regional cerebral metabolic rate of glucose (rCMRglc) providing an index of regional synaptic activity at rest and during experimental tasks.

PET measurements of rCBF or rCMRglc reflect mean regional synaptic activity over several tens of seconds ($H_2^{15}O$-PET of rCBF) or minutes (^{18}FDG-PET of rCMRglc). The low temporal resolution of PET requires that a continuous train or intermittent bursts of rTMS need to be given to cause a detectable change in regional neuronal activity. This implies that a single PET scan always represents the cumulative effects of individual stimuli on regional synaptic activity during the period of measurement. Therefore, combined TMS-PET measurements can readily capture cumulative changes in regional neuronal activity in the stimulated cortex and connected brain regions during prolonged trains of rTMS, because the neuronal effects of each stimulus can sum up during a single PET scan. Yet, the online TMS-PET approach is not suited to capture the effects of a single pulse or a short train of TMS on regional neuronal activity.

PET measurements of rCBF or rCMRglc during the administration of TMS have been used to map immediate TMS-induced changes in regional activity and connectivity independent of behaviour. This PET-TMS "perturb-and-measure" approach can assess how the spread of TMS-induced changes in neuronal activity depends on the intensity, frequency or site of TMS (Paus et al. 1997; Paus and Wolforth 1998; Siebner et al. 2001a, b; Speer et al. 2003a, 2003b).

The majorities of online TMS-PET studies were performed with the participants being at rest, but online TMS-PET imaging can also be used to examine how focal TMS interacts with the regional activation pattern during a specific task (Mottaghy et al. 2000, 2003). All currently available rTMS protocols can be given in the PET scanner because PET does not impose any temporal constraints on TMS. It is also easy to position the TMS coil over the cortical target area because there is sufficient space in the bore of the PET scanner.

4.3.2.2 Online TMS During Functional MRI

While technically easy to realise (Siebner et al. 2008, 2009a) the exposure to radiation as well as the inferior temporal resolution has limited the application of online TMS-PET to study brain connectivity. In contrast to PET, the combination of magnetic stimulation with BOLD-fMRI is technically demanding as both methods rely on strong magnetic fields. Bohning et al. (1998, 1999) were the first to establish interleaved TMS-fMRI as an experimental approach to map the acute effects of TMS on regional brain activity. Methodological refinements, such as the temporal separation of the administration of a TMS pulse from periods of MR image acquisition, are necessary to obtain good image quality and to ensure safety (Bestmann et al. 2008; Weiskopf et al. 2009). Moreover, the discharge of the TMS

coil in the scanner's static magnetic field intensifies auditory and sensory stimulation during TMS which requires appropriate control conditions.

Despite of these methodological challenges, concurrent TMS-fMRI has great potential to advance our understanding about the immediate and rapid changes TMS can evoke in cortical networks (Siebner et al. 2009a). Using an event-related design, the TMS-fMRI "perturb-and-measure" approach can reveal activity changes evoked by a single TMS pulse or a short TMS burst, by characterising TMS-evoked BOLD signal changes throughout the brain at rest (Bohning et al. 1998, 2000; Bestmann et al. 2003, 2004, 2005; Denslow et al. 2005). Here, TMS can be conceptualised as a means of injecting neural activity in the stimulated cortex and the resulting BOLD signal changes as a read out for the distributed activity changes. For instance, Bestmann et al. investigated the motor system while subjects were at rest. Even when stimulated at subthreshold intensities remote changes in neural activity occurred, both in cortical and subcortical sites (Bestmann et al. 2003, 2004). However, the direct site of stimulation showed BOLD activation only when being stimulated at comparatively high intensities (Bestmann et al. 2005), indicating a dissociation in sensitivity between electrophysiological and BOLD measures. Interestingly, focal TMS of the $M1_{HAND}$ induced a transient decrease in BOLD signal in the contralateral $M1_{HAND}$ which might represent a correlate for transcallosal inhibition (Bestmann et al. 2004). Moreover, a short high-frequent train of focal TMS applied over left PMD induced a transient increase in BOLD signal in connected brain regions such as right PMd, bilateral ventral premotor cortex (PMv), supplementary motor area, somatosensory cortex, cingulate motor area, left posterior temporal lobe, cerebellum and caudate nucleus. Responses were generally smaller during low-intensity rTMS showing that short trains of focal TMS can modify local hemodynamics in the absence of overt motor responses.

The TMS-fMRI "perturb-and-measure" approach can further be used to map state-dependent interregional interactions evoked by TMS during experimental tasks. Bestmann et al. (2005) acquired BOLD activation maps during concurrent application of a high-frequency TMS burst to left PMd at rest and during a hand grip task performed with the left hand. The TMS burst increased BOLD activity in contralateral PMd and $M1_{HAND}$ at high stimulation intensity (110 % of resting motor threshold) relative to TMS at a lower control intensity (70 % active motor threshold) when given at rest. This effect was reversed during the grip force task. Now high-intensity TMS facilitated task-related BOLD activity, compared with low-intensity TMS.

The same TMS-fMRI "perturb-and-measure" approach was also used to address the question whether the contralesional PMd supports residual motor function after subcortical motor stroke. To this end, TMS was given to contralesional PMd during fMRI to trace the causal influence of contralesional premotor TMS on the cortical motor network in either hemisphere and whether these influences changed during affected hand movement. In addition, dual-site TMS was used to assess the functional influence of contralesional PMd on corticospinal excitability in the ipsilesional $M1_{HAND}$. In patients with greater clinical and neurophysiological impairment, TMS of contralesional PMd had a stronger facilitatory influence on BOLD signal in posterior parts of ipsilesional sensorimotor cortex during the hand grip task. It was

argued that this state-dependent influence of contralesional PMd on ipsilesional sensorimotor regions may provide a mechanism by which the PMd contributes to functional recovery after stroke.

Concurrent TMS-fMRI has also been applied to investigate causal top-down influences between brain regions in the visual system and sensory processing: Ruff et al. (2006,2008) used TMS during fMRI to examine attentional top-down control of the frontal eye field or the intraparietal sulcus on task-related activation of posterior visual areas in top-down control of the visual cortex. Blankenburg et al. (2008) induced a decreased detection threshold with right parietal TMS indicating that TMS enhanced somatosensory processing of right hand input in left primary somatosensory cortex (S1). Concurrent BOLD fMRI indentified a corresponding task-related increase in BOLD signal in left SI with high-intensity TMS as opposed to low-intensity TMS. Right parietal TMS increased the BOLD signal in left S1 during right-wrist somatosensory input, but decreased the regional BOLD signal in the absence of somatosensory input. Another concurrent TMS-fMRI study identified cortical signatures of an TMS-evoked sense of movement after upper limb amputation (Bestmann et al. 2006). Together, these studies challenge the prevailing notion that the behavioural consequences of TMS (i.e., the "virtual lesion" effect) can exclusively be attributed to the disruptive effects of TMS at the stimulation site. These data rather suggest that remote activity changes induced by TMS in connected brain regions may contribute to or prevent the manifestation of behavioural consequences during online TMS.

4.3.3 Offline rTMS Before Neuroimaging: "The Condition-and-Map" Approach

As described in Sect. 4.2.3, a range of rTMS protocols is available to induce a lasting change in excitability in the stimulated cortex. These protocols can be used to induce acute reorganisation in functional brain networks. In this context, functional neuroimaging has great potential to map temporospatial patterns of functional reorganisation that are induced in the human brain by rTMS (Siebner et al. 2009a). This "condition-and-map" approach provides valuable insights into the changeability of functional brain networks. Neuroimaging should start shortly after the end of rTMS to ensure that short lasting after effects of rTMS are captured. Prolonged neuroimaging after conditioning rTMS can help to clarify how long the rTMS induced reorganisation persists. This also allows to address the question whether and how the rTMS-induced changes in brain activity and connectivity return back to the functional state at baseline.

With regard to fMRI, the "condition-and-map" approach is much easier to implement as compared to the "map-and-perturb" approach because rTMS and fMRI can be separated in time and space. In other words, TMS can simply be applied in a dedicated laboratory outside the MRI room. If functional neuroimaging is performed before and after the interventional rTMS protocol, it is necessary to

control for possible order and time effects. This can be achieved by adding a control session in which another rTMS protocol (e.g., sham rTMS, control rTMS over another cortical area, control rTMS at the same site but at lower intensity) is applied. Counterbalancing the order of the two sessions will provide an effective control for order effects (Siebner et al. 2009a).

Functional neuroimaging after a conditioning rTMS session may be performed during the resting state. Two recent studies (van der Werf et al. 2010; Eldaief et al. 2011) used the "condition-and-map" approach to investigate the impact of focal rTMS on resting-state connectivity in distinct resting-state networks, such as the default mode network (DMN). Eldaief et al. (2011) based their analysis on a priori information on six specific components of the DMN. They stimulated left posterior–inferior parietal lobule with two different frequencies (1 Hz vs. 20 Hz rTMS) and found frequency specific effects on functional connectivity between other network components and the hippocampal formation, suggesting the existence of different subcomponents of the network. Van der Werf et al. (2010) used an entirely data driven approach and extracted 41 resting-state networks using independent component analysis. One of these networks was the DMN which expressed resting-state connectivity in both, the sham condition (coil oriented in a way not resulting in actual stimulation) as well as the TMS condition (1 Hz rTMS over dorsal lateral prefrontal cortex). However, only after real 1Hz rTMS, the hippocampus did not appear as a network component.

Complementing studies on resting-state connectivity, other neuroimaging studies after rTMS have focussed on rTMS-induced changes in task-related functional connectivity. The experimental task should probe functional processing of those brain networks that have been targeted with rTMS. To demonstrate task specificity of functional reorganisation, it is useful to include an additional control task rather than a resting condition in the post-rTMS neuroimaging session. Lee et al. (2003) used $H_2\,{}^{15}O$ PET to assess changes in regional cerebral blood flow after 30 min of 1 Hz rTMS of left $M1_{HAND}$. Because they were interested in the acute rTMS-induced reorganisation of the healthy motor system, they mapped brain activity at rest and during a simple motor task which required subjects to generate externally paced but self selected button presses with the index, middle, ring or little finger of the right hand. "Inhibitory" 1 Hz rTMS increased synaptic activity in the stimulated left $M1_{HAND}$ at rest and during the motor task as well as movement-related activity in the PMd of the non-stimulated hemisphere. Analyses of functional connectivity revealed that the stimulated part of left $M1_{HAND}$ became less responsive to input from premotor and mesial motor areas. Conversely, the inferomedial portion of left $M1_{HAND}$ and premotor cortical areas showed increased functional coupling after 1 Hz rTMS. Since 1 Hz rTMS did not impair task performance, it was suggested that maintenance of task performance may involve activation of premotor areas contralateral to the site of rTMS along with acute remodelling of motor representations.

Offline fMRI has also been successfully employed to investigate short-term reorganisation of the motor system after 1 Hz rTMS to the left PMd (O'Shea et al. 2007). Subsequent fMRI revealed an activity increase in task-related activity during action selection in the non-stimulated right PMd. While 1 Hz rTMS of left PMd had

no effect on task performance during action selection, online TMS of the reorganised right PMd (after 1 Hz rTMS of left PMd) impaired action selection. Based on this finding, it was inferred that the functional reorganisation of right PMd as revealed by fMRI was functionally relevant to maintaining behaviour after 1 Hz rTMS of left PMd. In another offline rTMS-fMRI study, Ward et al. (2010) found that 30 min of 1 Hz rTMS over left rostral PMd had a beneficial effect on error rates when subjects had to dynamically adjust visuo-spatial response mapping. The decrease in error rate after 1 Hz rTMS was correlated with a left-hemispheric increase in functional connectivity between the stimulated PMd and the anterior supramarginal gyrus.

Raclopride PET of postsynaptic striatal D2 receptor binding has been performed after a conditioning rTMS session. These studies have demonstrated that the repeated application of high-frequency rTMS to a cortical area causes a lasting increase in endogenous dopamine release in the striatal projection region of the stimulated cortex (Strafella et al. 2001, 2003). This work highlights the potential of offline PET to assess the conditioning effects of rTMS on specific neurotransmitters systems.

The "conditioning-and-mapping" approach has also been used to study pathological conditions (Rowe and Siebner 2012). In focal hand dystonia, 1 Hz rTMS of left PMd induced a greater decrease in regional neural activity in lateral and medial premotor areas, putamen and thalamus, revealing increased spread of the conditioning effects of rTMS throughout the motor system in focal hand dystonia (Siebner et al. 2003) relative to healthy controls. In patients with pure subcortical stroke without cortical involvement, facilitatory 10 Hz rTMS over ipsilesional $M1_{HAND}$ improved motor function and reduced neural activity in contralesional $M1_{HAND}$ (Ameli et al. 2009). The same group mapped the BOLD correlates of improved motor performance after inhibitory 1 Hz rTMS over contralesional $M1_{HAND}$ in subcortical stroke. DCM revealed that motor improvement was associated with short-term motor reorganisation (Grefkes et al. 2010): Contralesional 1 Hz rTMS attenuated the negative transcallosal influence of contralesional $M1_{HAND}$ on ipsilesional $M1_{HAND}$ along with a reinforcement of ipsilesional effective connectivity between SMA and $M1_{HAND}$. These examples underscore the potential of the "condition-and-map" approach to uncover rTMS-induced changes in the causal interplay among interconnected motor brain regions. The "condition-and-map" approach can also make substantial contributions to advance our understanding how these causal dynamics contribute to brain function or dysfunction and how they mediate functional improvement in response to therapeutic interventions.

References

Ameli M, Grefkes C et al (2009) Differential effects of high-frequency repetitive transcranial magnetic stimulation over ipsilesional primary motor cortex in cortical and subcortical middle cerebral artery stroke. Ann Neurol 66(3):298–309

Baumer T, Bock F et al (2006) Magnetic stimulation of human premotor or motor cortex produces interhemispheric facilitation through distinct pathways. J Physiol 572(Pt 3):857–868

Bestmann S, Baudewig J et al (2003) Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. Neuroimage 20(3):1685–1696
Bestmann S, Baudewig J et al (2004) Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci 19(7):1950–1962
Bestmann S, Baudewig J et al (2005) BOLD MRI responses to repetitive TMS over human dorsal premotor cortex. Neuroimage 28(1):22–29
Bestmann S, Oliviero A et al (2006) Cortical correlates of TMS-induced phantom hand movements revealed with concurrent TMS-fMRI. Neuropsychologia 44(14):2959–2971
Bestmann S, Ruff CC et al (2008) Mapping causal interregional influences with concurrent TMS-fMRI. Exp Brain Res 191(4):383–402
Biswal B, Yetkin FZ et al (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34(4):537–541
Blankenburg F, Ruff CC et al (2008) Interhemispheric effect of parietal TMS on somatosensory response confirmed directly with concurrent TMS-fMRI. J Neurosci 28(49):13202–13208
Bohning DE, Shastri A et al (1998) Echoplanar BOLD fMRI of brain activation induced by concurrent transcranial magnetic stimulation. Invest Radiol 33(6):336–340
Bohning DE, Shastri A et al (1999) A combined TMS/fMRI study of intensity-dependent TMS over motor cortex. Biol Psychiatry 45(4):385–394
Bohning DE, Shastri A et al (2000) BOLD-f MRI response to single-pulse transcranial magnetic stimulation (TMS). J Magn Reson Imaging 11(6):569–574
Boorman ED, O'Shea J et al (2007) Individual differences in white-matter microstructure reflect variation in functional connectivity during choice. Curr Biol 17(16):1426–1431
Buchel C, Friston KJ (1998) Dynamic changes in effective connectivity characterized by variable parameter regression and Kalman filtering. Hum Brain Mapp 6(5–6):403–408
Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10(3):186–198
Damoiseaux JS, Greicius MD (2009) Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct Funct 213(6):525–533
Davare M, Lemon R et al (2008) Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans. J Physiol 586(Pt 11):2735–2742
Davare M, Rothwell JC et al (2010) Causal connectivity between the human anterior intraparietal area and premotor cortex during grasp. Curr Biol 20(2):176–181
Deco G, Jirsa VK et al (2011) Emerging concepts for the dynamical organization of resting-state activity in the brain. Nat Rev Neurosci 12(1):43–56
Denslow S, Lomarev M et al (2005) Cortical and subcortical brain effects of transcranial magnetic stimulation (TMS)-induced movement: an interleaved TMS/functional magnetic resonance imaging study. Biol Psychiatry 57(7):752–760
Deshpande G, Sathian K et al (2010) Effect of hemodynamic variability on Granger causality analysis of fMRI. Neuroimage 52(3):884–896
Eldaief MC, Halko MA et al (2011) Transcranial magnetic stimulation modulates the brain's intrinsic activity in a frequency dependent manner. Proc Natl Acad Sci USA PMID: 22160708
Ferbert A, Priori A et al (1992) Interhemispheric inhibition of the human motor cortex. J Physiol 453:525–546
Fox P, Ingham R et al (1997) Imaging human intra-cerebral connectivity by PET during TMS. NeuroReport 8(12):2787–2791
Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8(9):700–711
Friston KJ (1994) Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 2(1–2):56–78
Friston K (2009) Causal modelling and brain connectivity in functional magnetic resonance imaging. PLoS Biol 7(2):e33

Friston KJ (2011) Functional and effective connectivity: a review. Brain Connectivity 1(1):13–36
Friston KJ, Harrison L et al (2003) Dynamic causal modelling. Neuroimage 19(4):1273–1302
Friston KJ, Li B et al (2011) Network discovery with DCM. Neuroimage 56(3):1202–1221
Grefkes C, Nowak DA et al (2010) Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. Neuroimage 50(1):233–242
Greicius MD, Supekar K et al (2009) Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex 19(1):72–78
Groppa S, Schlaak BH et al (2011) The human dorsal premotor cortex facilitates the excitability of ipsilateral primary motor cortex via a short latency cortico cortical route. Hum Brain Mapp
Gusnard DA, Raichle ME (2001) Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2(10):685–694
Hagmann P, Cammoun L et al (2010) MR connectomics: Principles and challenges. J Neurosci Methods 194(1):34–45
Hampson M, Shen X et al (2012) Functional connectivity MR imaging. In: Faro SH, Mohamed FB (eds) Functional Neuroradiology: Principles and Clinical Applications (in press)
Honey CJ, Sporns O et al (2009) Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci U S A 106(6):2035–2040
Hubers A, Klein JC et al (2011) The relationship between TMS measures of functional properties and DTI measures of microstructure of the corticospinal tract. Brain Stimul 32:846–855
Johansen-Berg H (2010) Behavioural relevance of variation in white matter microstructure. Curr Opin Neurol 23(4):351–358
Johansen-Berg H, Rushworth MF (2009) Using diffusion imaging to study human connectional anatomy. Annu Rev Neurosci 32:75–94
Kloppel S, Baumer T et al (2008) The cortical motor threshold reflects microstructural properties of cerebral white matter. Neuroimage 40(4):1782–1791
Koch G, Franca M et al (2006) Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. J Neurosci 26(28):7452–7459
Koch G, Franca M et al (2007) Interactions between pairs of transcranial magnetic stimuli over the human left dorsal premotor cortex differ from those seen in primary motor cortex. J Physiol 578(Pt 2):551–562
Koch G, Fernandez Del Olmo M et al (2008) Functional interplay between posterior parietal and ipsilateral motor cortex revealed by twin-coil transcranial magnetic stimulation during reach planning toward contralateral space. J Neurosci 28(23):5944–5953
Lee L, Siebner HR et al (2003) Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J Neurosci 23(12):5308–5318
Li B, Daunizeau J et al (2011) Generalised filtering and stochastic DCM for fMRI. Neuroimage 58(2):442–457
Mochizuki H, Huang YZ et al (2004) Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. J Physiol 561(Pt 1):331–338
Mottaghy FM, Krause BJ et al (2000) Modulation of the neuronal circuitry subserving working memory in healthy human subjects by repetitive transcranial magnetic stimulation. Neurosci Lett 280(3):167–170
Mottaghy FM, Pascual-Leone A et al (2003) Modulation of a brain-behavior relationship in verbal working memory by rTMS. Brain Res Cogn Brain Res 15(3):241–249
Ogawa S, Lee TM et al (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 87(24):9868–9872
O'Shea J, Johansen-Berg H et al (2007) Functionally specific reorganization in human premotor cortex. Neuron 54(3):479–490
Pascual-Leone A, Walsh V et al (2000) Transcranial magnetic stimulation in cognitive neuroscience–virtual lesion, chronometry, and functional connectivity. Curr Opin Neurobiol 10(2):232–237
Pastor J, Lafon M et al (2000) Information processing in large-scale cerebral networks: the causal connectivity approach. Biol Cybern 82(1):49–59
Paus T (2005) Inferring causality in brain images: a perturbation approach. Philos Trans R Soc Lond B Biol Sci 360(1457):1109–1114

Paus T, Wolforth M (1998) Transcranial magnetic stimulation during PET: reaching and verifying the target site. Hum Brain Mapp 6(5–6):399–402

Paus T, Jech R et al (1997) Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J Neurosci 17(9):3178–3184

Paus T, Jech R et al (1998) Dose-dependent reduction of cerebral blood flow during rapid-rate transcranial magnetic stimulation of the human sensorimotor cortex. J Neurophysiol 79(2):1102–1107

Raichle ME, Snyder AZ (2007) A default mode of brain function: a brief history of an evolving idea. Neuroimage 37(4):1083–1090 discussion; 1097–1089

Raichle ME, MacLeod AM et al (2001) A default mode of brain function. Proc Natl Acad Sci U S A 98(2):676–682

Roebroeck A, Formisano E et al (2005) Mapping directed influence over the brain using Granger causality and fMRI. Neuroimage 25(1):230–242

Rogers BP, Morgan VL et al (2007) Assessing functional connectivity in the human brain by fMRI. Magn Reson Imaging 25(10):1347–1357

Rowe JB, Siebner HR (2012) The motor system. NeuroImage 61(2):464–477

Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52(3):1059–1069

Ruff CC, Blankenburg F et al (2006) Concurrent TMS-fMRI and psychophysics reveal frontal influences on human retinotopic visual cortex. Curr Biol 16(15):1479–1488

Ruff CC, Bestmann S et al (2008) Distinct causal influences of parietal versus frontal areas on human visual cortex: evidence from concurrent TMS-fMRI. Cereb Cortex 18(4):817–827

Sach M, Winkler G et al (2004) Diffusion tensor MRI of early upper motor neuron involvement in amyotrophic lateral sclerosis. Brain 127(Pt 2):340–350

Scholz J, Klein MC et al (2009) Training induces changes in white-matter architecture. Nat Neurosci 12(11):1370–1371

Siebner HR, Rothwell J (2003) Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res 148(1):1–16

Siebner HR, Willoch F et al (1998) Imaging brain activation induced by long trains of repetitive transcranial magnetic stimulation. NeuroReport 9(5):943–948

Siebner H, Peller M et al (2001a) Activation of frontal premotor areas during suprathreshold transcranial magnetic stimulation of the left primary sensorimotor cortex: a glucose metabolic PET study. Hum Brain Mapp 12(3):157–167

Siebner HR, Takano B et al (2001b) Continuous transcranial magnetic stimulation during positron emission tomography: a suitable tool for imaging regional excitability of the human cortex. Neuroimage 14(4):883–890

Siebner HR, Filipovic SR et al (2003) Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. Brain 126(Pt 12):2710–2725

Siebner H, Peller M, et al (2008) TMS and positron emission tomography: methods and current advances. In:Wassermann E, Epstein C, Ziemann et al U (eds), The Oxford handbook of transcranial stimulation Oxford University Press, Oxford, pp 549–567

Siebner HR, Bergmann TO et al (2009a) Consensus paper: combining transcranial stimulation with neuroimaging. Brain Stimul 2(2):58–80

Siebner HR, Hartwigsen G et al (2009b) How does transcranial magnetic stimulation modify neuronal activity in the brain? Implications for studies of cognition. Cortex 45(9):1035–1042

Silvanto J, Muggleton NG et al (2007) Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation. Eur J Neurosci 25(6):1874–1881

Speer AM, Willis MW et al (2003a) Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with $H2^{15}O$ positron emission tomography: I. Effects of primary motor cortex rTMS. Biol Psychiatry 54(8):818–825

Speer AM, Willis MW et al (2003b) Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with

$H2^{15}O$ positron emission tomography: II. Effects of prefrontal cortex rTMS. Biol Psychiatry 54(8):826–832

Sporns O, Chialvo DR et al (2004) Organization, development and function of complex brain networks. Trends Cogn Sci 8(9):418–425

Sporns O, Tononi G et al (2005) The human connectome: a structural description of the human brain. PLoS Comput Biol 1(4):e42

Strafella AP, Paus T et al (2001) Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. J Neurosci 21(15):RC157

Strafella AP, Paus T et al (2003) Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 126(Pt 12):2609–2615

van der Werf YD, Sanz-Arigita EJ et al (2010) Modulating spontaneous brain activity using repetitive transcranial magnetic stimulation. BMC Neurosci 11:145

Wahl M, Lauterbach-Soon B et al (2007) Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. J Neurosci 27(45):12132–12138

Walsh V, Rushworth M (1999) A primer of magnetic stimulation as a tool for neuropsychology. Neuropsychologia 37(2):125–135

Ward NS, Bestmann S et al (2010) Low-frequency transcranial magnetic stimulation over left dorsal premotor cortex improves the dynamic control of visuospatially cued actions. J Neurosci 30(27):9216–9223

Weiskopf N, Josephs O et al (2009) Image artifacts in concurrent transcranial magnetic stimulation (TMS) and fMRI caused by leakage currents: modeling and compensation. J Magn Reson Imaging 29(5):1211–1217

Ziemann U, Paulus W et al (2008) Consensus: motor cortex plasticity protocols. Brain Stimul 1(3):164–182

Chapter 5
Accessing Cortical Connectivity Using TMS: EEG Co-registration

TMS and Connectivity

Carlo Miniussi, Marta Bortoletto, Gregor Thut and Domenica Veniero

Abstract The combination of brain stimulation by transcranial magnetic stimulation (TMS) with simultaneous electroencephalographic (EEG) recording has the potential to be of great value for understanding the cortico-cortical connections within brain networks and how they are linked to cognitive or motor functions. It can reveal how connectivity varies as a function of neuronal state, differing between individuals and patient groups. In this chapter, we will first provide an historical overview on the development of the TMS-EEG co-registration methodology and highlight the technical challenges that need to be faced for its application. We will then discuss the wide range of possible TMS-EEG co-registration techniques and what new information may be gained on the dynamics of brain functions, hierarchical organization, and cortical connectivity, as well as on the action of TMS action per se. An advance in the understanding of these issues is timely and promises to have a substantial impact on many areas of clinical and basic neuroscience.

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5.1 Introduction

Our knowledge on how different areas of the brain interact with each other and how these interactions change while subjects perform different tasks, or learn new skills, is mainly based on correlations rather than on precise cause-effect relationships. Several neuroimaging techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG), allow to demonstrate associations between a given cognitive state and the measured patterns of brain activity. Nevertheless, the activation of an area, or a network, during a task is not sufficient to conclude that the activated areas are crucial to the involved function. Rather, it is necessary to demonstrate that the manipulation of activity in these same areas leads to changes in task performance (Bailey et al. 2001).

Transcranial brain stimulation allows for exactly this. Available techniques include transcranial magnetic stimulation (TMS) (Wassermann et al. 2008) and transcranial electrical stimulation (tES) (Nitsche et al. 2008). These techniques have gained popularity as mapping tools for studying perceptual, motor, and cognitive functions in the human brain due to their unique potential to investigate the state of targeted brain areas and/or their causal involvement in a specific function. They allow for manipulation of activity in areas of the superficial brain as an independent variable (Sack and Linden 2003) and because of this advantage, their fields of application are ever growing (Fregni and Pascual-Leone 2007; Hummel and Cohen 2006; Miniussi et al. 2008, 2010; Miniussi and Rossini 2012; Ridding and Rothwell 2007; Walsh and Cowey 2000).

Moreover, thanks to the implementation of new paradigms and new techniques for co-registering brain activity during stimulation, i.e., with EEG and fMRI, transcranial brain stimulation allows the study of functional connectivity within brain networks. Indeed, transcranial brain stimulation not only activates the targeted brain area but also areas that are anatomically and functionally connected to the target site, and thereby alters their interactions, which can transiently influence behavior.

Traditionally, TMS effects have been quantified with two different outcome measures: peripheral indices and behavioral performance. The first measure is limited to studies performed on motor areas. It is based on the fact that TMS, when delivered over the primary motor cortex with adequate intensity, activates the corticospinal tract resulting in a muscle twitch in the target muscle, named motor evoked potential (MEP). TMS effects are inferred from changes in the amplitude of these MEPs, or other features of the peripheral response, such as motor threshold, duration of silent period or spinal reflexes (Quartarone et al. 2005; Valero-Cabre and Pascual-Leone 2005) (for a discussion of the potentials of these application, see Chaps. 2, 9 and 10). The second traditional approach consists of evaluating the impact of TMS on the participant's performance in a specific task (Hilgetag et al. 2001; Pascual-Leone et al. 1994; Ruzzoli et al. 2010; Sandrini et al. 2010; Thut et al. 2005; Valero-Cabre et al. 2006) while the area considered to be engaged in the task is stimulated either directly or indirectly (by TMS over a connected site).

These two approaches of dealing with TMS-induced effects have provided an impressive amount of data, but are limited in that they do not reveal how TMS affects the stimulated area and its functioning within the whole neural network. In particular, MEPs are the result of complex events and necessarily depend on the state of different elements along the corticospinal pathway. While the "behavioural" approach has the limitation of inferring cortical effects of TMS from an indirect measure, usually reaction times or accuracy. Therefore, purely behavioral TMS studies may not reveal whether the effects primarily arise from interference with the site of stimulation, or may additionally involve interconnected brain regions.

Given these limitations, it has been advocated that alternative approaches in the use of TMS should be considered to study brain functioning and network connectivity. To this end, TMS has been combined with neuroimaging techniques such as fMRI and PET, as well as with EEG. This assists the interpretation of TMS impact upon the brain both in healthy humans and patients by providing objective and direct measurements of brain activity. This multimodal imaging approach has several advantages (Siebner et al. 2009; see also Chap. 4). First, it permits assessment of the local impact of TMS on neural processing by means of objective measures of cortical reactivity, i.e., over the directly targeted area. Second, it provides an assessment of remote effects of TMS, i.e., on neural processing in distal brain regions. Crucially, the local activation caused by the magnetic pulse is expected to spread to connected areas, which can be traced by simultaneous fMRI, PET, or multichannel EEG recording. When applied in an experimental context in which the cognitive state of the subject or the physiological state of the brain are modulated, this approach allows direct demonstration of which areas are functionally linked during a task, or how a given state shapes cortical connectivity.

Besides being a tool for evaluating cortical reactivity and connectivity, TMS can also be used to modulate brain functions in humans. Using multimodal imaging, it becomes then possible to directly monitor in vivo the neuronal consequences and eventually associated behavioral changes of stimulating an area of the cortex. Therefore, the multimodal imaging approach, such as the combination of TMS with EEG, overcomes some of the limitations of single techniques. It supplements the information provided by correlational analyses (e.g., on task-related EEG changes) with a technique that can establish a causal link between brain activity and behavior, and allows to evaluate these causal effects in the entire brain.

It is feasible to combine TMS with PET, fMRI, and EEG. Which combination to select depends on the specific aims of the study. Each combination focuses on different aspects of TMS-induced changes in brain activity. TMS-PET and TMS-fMRI co-registration are of interest because these techniques can in principle reveal the spatial profiles of transcranial brain stimulation effects with high spatial resolution, including in subcortical structures ipsilateral and contralateral to the stimulation site (Siebner et al. 2009). Nevertheless, these techniques are based on changes in blood flow and oxygenation, which typically occur a few seconds after changes in neuronal activity. They therefore have a reduced temporal resolution and can only detect modulations arising a few seconds (fMRI) or even minutes (PET) post-stimulus. Given that TMS-induced brain activity occurs within a few

hundreds of milliseconds after the TMS impulse, these techniques do not address the high temporal resolution window during which profound and functionally relevant TMS-induced neural events are thought to take place (Bonato et al. 2006; Komssi and Kahkonen 2006).

When the timing of the TMS-induced cortical activity is relevant, EEG provides a suitable method to complement TMS. In addition and possibly as a result of this high temporal resolution, EEG seems particularly sensitive in revealing the neuronal effects of TMS. For example, BOLD MRI does not detect any changes in brain activity when TMS is delivered at subthreshold intensities, i.e., at about 80 % of motor threshold (Bohning et al. 1999). In contrast, it has been shown that several TMS-evoked responses can be recorded by EEG when TMS is administered at 40 % of resting motor threshold (Komssi et al. 2007). Additionally, thanks to computer technology that enabled the development of portable EEG recording, TMS-EEG is also a promising neurophysiological technique that is feasible at the patients' bedside for diagnostics purposes and may have clinical utility. However, EEG has a poor spatial resolution and the cortical localization of the TMS effects can only be inferred from source localization algorithms.

5.2 Early TMS-EEG Studies

The first attempt of TMS-EEG co-registration was reported in 1989 by Cracco and collaborators (1989) who investigated inter-hemispheric transcallosal conduction time. Activity was recorded from an electrode placed over the left premotor cortex (between F3 and C3, corresponding to the posterior part of the middle frontal gyrus, Brodmann area 6), while stimulating the homologous contralateral site. A positive deflection was reported contralateral to stimulation peaking at 9–12 ms after the TMS pulse (Cracco et al. 1989).

Subsequently, only one paper reported the use of TMS-EEG (Amassian et al. 1992) until 1997, when a new generation of amplifiers was introduced (Ilmoniemi et al. 1997; Virtanen et al. 1999). The reason why this approach was not applied was related to technical limitations and saturation of the EEG recording system caused by the strong electromagnetic pulse. Ilmoniemi et al. (1997) reported for the first time TMS-induced activity recorded with multichannel EEG (60 recording electrodes). Their TMS-EEG co-registration system was equipped with a sample-and-hold circuit that could block the EEG amplifier signal for a few micro- to milliseconds for the duration of the TMS discharge (for similar approach see also Iramina and Maeno 2003; Taylor et al. 2007b; Virtanen et al. 1999). This avoids saturation of the recording amplifiers by the electromagnetic pulse, allowing the recording of EEG activity shortly after TMS delivery.

Since then, several groups have applied this methodology (see e.g., Komssi and Kahkonen 2006). Other amplifiers that are not saturating but allow continuous data recording throughout TMS have also been tested and successfully used (e.g., Bonato et al. 2006; Fuggetta et al. 2006; Ives et al. 2006; Taylor et al. 2010;

Veniero et al. 2010). This has led to reports of several possible applications (Komssi and Kahkonen 2006; Siebner et al. 2009; Taylor et al. 2008; Thut and Miniussi 2009). Nowadays, it is therefore possible to run continuous EEG recordings during TMS stimulation. Nevertheless, this new technology still poses some problems related to the very high-energy component of the TMS pulse that we will review in the following section.

5.3 The Basics of EEG-TMS Studies

The TMS pulse has a very high-energy component and it most likely induces charges in electrodes, leads, amplifiers, and skin that last longer than the TMS pulse. Therefore, at least part of the initial large response recorded after TMS stimulation is due to non-cortical currents induced by the magnetic field.

In several papers, it was reported that it is not possible to record a clear EEG signal in the first 30–300 ms after TMS (Bender et al. 2005; Morbidi et al. 2007; Taylor et al. 2008; Thut et al. 2003). Several reasons can account for the long-lasting TMS artifact. The main reason may be that electrodes and skin have magnetic properties, and may therefore be affected by the TMS pulse and generate non-cortical signals in the recording. EEG is traditionally performed with electrodes made of tin, silver, silver-chloride, or gold, with a fairly large and ring-shaped surface. This standard electrodes permit eddy currents to be generated during TMS, which can cause heating or even movement of the electrodes. In terms of safety, this poses a risk of scalp burns under the electrode (Pascual-Leone et al. 1990, 1993; Rossi et al. 2009; Roth et al. 1992; Veniero et al. 2009). With regard to signal quality, heating and movement can induce electrical artifacts and reduce the signal to noise ratio. Eddy currents and therefore overheating of the electrodes located in the vicinity of the stimulating coil may be minimized by cutting out a section of the ring metal electrodes to create a radial notch (Roth et al. 1992). Plastic electrodes have also been used (Ives et al. 2006) but with a conductive-silver epoxy coat. Moreover, it has been shown that by using TMS-compatible pellet electrodes, it is possible to obtain the same result without cutting the electrodes (Virtanen et al. 1999, 2009).

To resolve this artifact issue, several procedures have been proposed. Subtraction approaches are based on creating templates of the TMS-induced artifact by collecting data while TMS is applied on a phantom (Bender et al. 2005) or in a condition that does not involve a task (Thut et al. 2003). To isolate brain signals from the TMS-induced artifacts, the template is then subtracted from data collected in the experimental condition, in which TMS is applied during a task. Moreover, if in some electrodes the signal is irremediably contaminated by the TMS artifact, these electrodes can be excluded from further analyses (Komssi et al. 2004). Other, alternative solutions to remove TMS-induced artifacts are based on filtering methods (Morbidi et al. 2007), principal component analysis (Litvak et al. 2007), and independent component analysis (Hamidi et al. 2010).

To establish optimal conditions for recording EEG during TMS, Veniero et al. (2009) studied artifact-inductions while systematically manipulating various technical parameters (TMS pulse configurations, TMS coils, EEG settings, electrode impedance, wire orientation). Note that the parameter space was explored for a TMS-compatible EEG system that allows continuous recordings. Information on absolute artifact-duration may only apply for this particular system, but relative differences across parameters should generalize to other systems. To better characterize the TMS artifact and to exclude any physiological response, recordings were performed with TMS of a phantom 'head' and then compared to the recordings obtained from knee stimulation and cortical stimulation. EEG signal was acquired at 5,000 Hz and band-passed at 0.01–1,000 Hz. Different types of TMS pulse configurations and stimulators (monophasic, biphasic with four boosters, and biphasic with single power supply module), different TMS coils (four figure-of-eight coils, i.e., standard 50–70 mm, custom 25–70 mm), several TMS intensities (ranging from 10 to 100 % of the stimulator output), and frequencies of stimulation (single pulse, 5 Hz and 20 Hz) were compared. The main results indicated that, regardless of the above-cited parameters, TMS-induced artifact always lasted about 5–6 ms, as can been seen in Fig. 5.1. One critical variable influencing artifact-duration was the choice of the EEG acquisition settings. Lower sampling rate and filters caused rippling of the signal, and an increase in the duration of the TMS-induced artifact, preventing the sampling of information shortly after the pulse. Moreover, the impendence values of EEG electrodes also played an important role in artifact contamination, as it was found that for high impedances (about 20 kΩ), EEG signal recovery time was slower (15–20 ms) and artifact amplitude was higher (>two times) than for lower impedances (0–3 kΩ) (see also Julkunen et al. 2008b).

Besides the above described TMS-artifact, EEG signals can also be contaminated several tens of milliseconds after the TMS pulse with a coil-recharge-artifact that is present with biphasic but not monophasic stimulators (Veniero et al. 2009). Finally, to keep the artifact minimal, Veniero et al. (2009), found that the wires should be arranged in an orientation away from the coil or coil cable, regardless of where stimulation takes place on the head. The reorientation of the wires before stimulation can therefore help to record clearer signals (see also Sekiguchi et al. 2011).

Apart from optimizing recording parameters, it is important to consider that TMS can also induce nonspecific or indirect brain responses, which may influence the EEG recording (Komssi and Kahkonen 2006; Miniussi and Thut 2010; Taylor et al. 2008). These nonspecific, task unrelated contaminations consist of (i) auditory responses due to the coil click; (ii) somatosensory responses mostly due to trigeminal afferents or afferent responses after motor cortex stimulation; and (iii) muscular responses because of eye blinks and startle induced by the coil click, and peripheral muscular contractions due to peripheral stimulation. Also, general arousal due to TMS or auditory intersensory facilitation induced by the coil click might be present. All these effects should be eliminated or masked whenever possible (e.g., Massimini et al. 2005). In instances where this is not possible, these artifacts should, as part of the experimental design, be reproduced in separate conditions (i.e., via control stimulation at appropriate sites), and their effects should be taken into account during data analysis and interpretation.

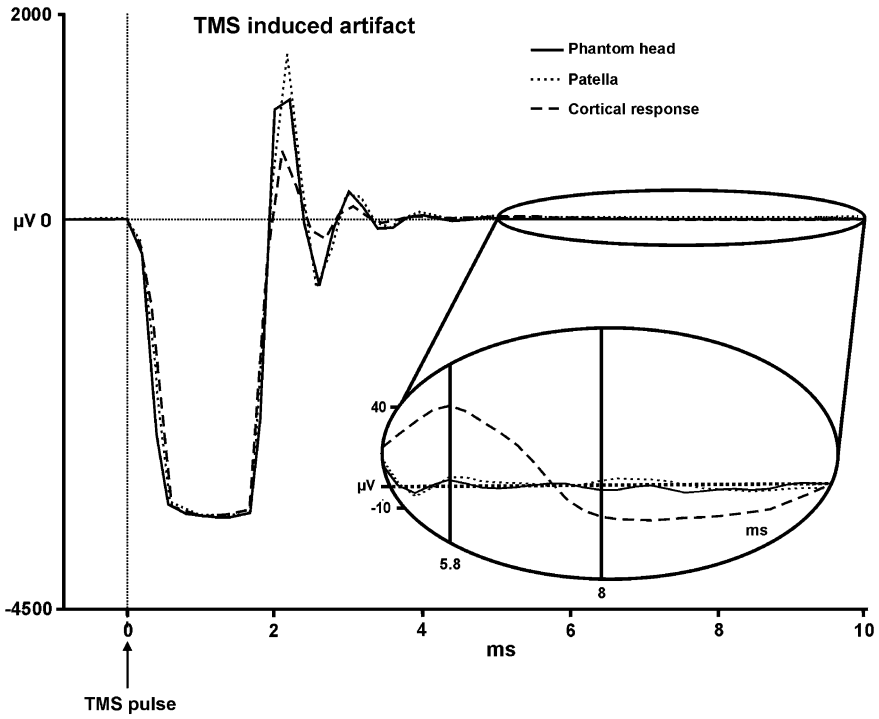

Fig. 5.1 TMS-induced artifact as recorded from three different models: the phantom head, patella and cortical stimulation. The stimulus intensity was set at 50 and 40 % of maximum stimulator output (MSO) as well as at individual resting motor threshold (57 % of MSO), respectively. Signal from the phantom and patella was recorded from the electrode beneath the coil, while the cortical response was acquired from Cz. The EEG recorded from 5 to 10 ms is magnified for clear visualization (from Veniero et al. 2009)

5.4 Instruction of Use

In the last few years, the TMS-EEG co-registration has been applied to study the brain from different perspectives. These will be described below along three main lines of applications (recently proposed by Miniussi and Thut 2010), the inductive, interactive, or rhythmic TMS-EEG approach.

5.4.1 Inductive Approach: Connectivity and TMS-Evoked Potentials

In the inductive approach, which also represents the first EEG-TMS application used (Ilmoniemi et al. 1997), TMS-evoked potentials (TEPs) are measured from the scalp while subjects are in a resting state, i.e., they are not performing any task (Bonato et al. 2006; Esser et al. 2006; Ilmoniemi et al. 1997; Iramina and Maeno

2003). The rationale for using an inductive approach is to probe the state of the cortex and to evaluate cortical excitability and connectivity. Cortical excitability is probed by studying the reactivity of the target area (usually in response to a single TMS pulse), the amplitude of the TEPs being dependent on the stimulation intensity, thus reflecting the reactivity of the stimulated cortex (Komssi et al. 2004, 2007). In analogy to MEPs, TEPs represent quantifiable markers of cortical excitability. However, TEPs have three crucial advantages over MEPs. First, TEPs are a direct measure of cortical reactivity, whereas, MEPs are a peripheral index that can be influenced by other factors. Second, TEPs allow investigation of the areas considered behaviorally silent, i.e., areas where stimulation does not yield directly observable behavioral effects. Third, TEPs provide a method to investigate brain connectivity (Komssi et al. 2002; Massimini et al. 2005) in normal participants, and in neurological and psychiatric disorders. Indeed, when a cortical region is stimulated, the spreading of the induced activity can be traced by means of the distribution of the EEG signals over the scalp, or their cortical source reconstruction.

TEP-components and TEP-topographies are one of the simplest ways to evaluate cortico-cortical connectivity with TMS–EEG co-registration. For example, using the same approach that has been used to evaluate interhemispheric transfer of information (Ipata et al., 1997), it should be possible to subtract the latency of TEP-components evoked by TMS of a given area from the latency of the same components evoked by the stimulation of the contralateral homologous area. This will give the possibility to estimate the interhemispheric transfer time between two areas that are considered to be directly connected. Nevertheless, we would expect that activity spreads not only between homologous areas. Therefore, to be able to track signal spreading across the cerebral cortex, more complex analyses must be carried out, such as the use of EEG source localization algorithms.

This approach was implemented by Ilmoniemi et al. (1997) (but see also Komssi et al. 2002) who computed activation maps from TEPs using minimum-norm estimates. The analysis was focused on the waveform, latency, and cortical distribution of TEPs. Ilmoniemi et al. (1997) showed that TMS of motor cortex induced a direct activation of the stimulated motor area (at latencies of 3 and 10 ms), followed by a spreading of neuronal activation to ipsilateral premotor areas and then to the contralateral hemisphere (at 24 ms).

Precise sources localization of TEP-components was performed by Litvak et al. (2007). Using a multiple source dipole model, they found an ipsilateral activation of the stimulated motor cortex, of the cingulate gyrus/supplementary motor cortex as well as of the cerebellum. Litvak et al. (2007) provided a direct demonstration that it is possible to implement the spatio-temporal decomposition approach to identify singular nodes of the probed network.

A few studies have employed the inductive approach to evaluate altered connectivity in diseases such as Alzheimer disease (AD) (Julkunen et al. 2008a) and as a tool for diagnostics and early identification of mild cognitive impairment (MCI). Julkunen et al. (2008a) showed that stimulation of the motor cortex in AD patients was associated with prominent changes in functional cortical connectivity. Namely, they found a significant decrease in the TMS-induced activity over

several brain areas in AD patients compared with healthy controls, suggesting a dysfunction of a large-scale sensorimotor network.

Moreover, the inductive approach has been successfully applied in numerous studies to investigate cortical connectivity as a function of different physiological states of the subject. For example, Kahkonen et al. (2001) used this approach to evaluate how cortical responses can change based on the "modulation" of the physiological state with ethanol consumption. Cortical distribution of TEPs was evaluated in a group of subjects before and after ethanol consumption. Results showed mainly prefrontal differences in TEP maps before as compared to after ethanol ingestion. The data revealed that ethanol consumption can change the functional connectivity between prefrontal and motor cortices providing direct evidence that the modulation of cortical connectivity can depend on the physiological state of the nervous system.

Zanon et al. (2010) investigated the spreading of activity from the left parietal cortex to prefrontal regions in healthy volunteers. Their findings suggest that the parietal regions are connected with the contra-lateral prefrontal regions and that this connection was activated in a time range of 100–170 ms after the TMS. Moreover, they revealed a connection between parietal regions and the ipsilateral temporo-occipital cortex, showing that it was possible to track the presence of specific contra- as well as ipsilateral cortical connections. However, volunteers were asked to stay in a rest position with closed eyes. It is therefore difficult to draw a specific conclusion about functional connectivity among parietal cortex and other regions in other physiological states.

In a similar study on connectivity, Massimini and colleagues (Ferrarelli et al. 2010; Massimini et al. 2005) stimulated the premotor cortex of subjects while they were in different states (i.e., awake or sleeping) in order to evaluate how state influences connectivity. In both conditions, the local TEPs were similar, whereas the remote responses differed dramatically. During wakefulness, TMS induced activity spread within and between hemispheres, whereas during sleep, activity remained confined to regions surrounding the stimulated area.

The importance of these studies is that they illustrate how effective connectivity (i.e., the functional interactions between distinct elements within a nervous system) changes depending on the state of the subject. This introduces the concept that cortical connections of a stimulated area cannot be considered to be independent from its functional status (Ferrarelli et al. 2010; Massimini et al. 2005). These aspects suggest that the functional effects induced in one area could be co-opted into different functions depending on the state of activation (state dependency) or which of its interconnected networks were activated (e.g., Harris et al. 2008; Selimbeyoglu and Parvizi 2010; Silvanto et al. 2005).

5.4.2 Interactive Approach: Cortical Connectivity While the Subject is Performing a Task

The interactive approach refers to EEG-TMS experiments in which subjects are asked to perform a task and TMS is used to interact with a specific brain region

thought to be involved in a given function. In this case, EEG is used to reveal the network affected by TMS (which could involve the targeted area, any interconnected region, or both), to measure the timing of the induced activity changes and how the TMS-induced perturbation correlates with performance (Miniussi and Thut 2010; Taylor et al. 2008). The rationale of this approach is to gain insights into how neural areas interact during task preparation and execution (Nikulin et al. 2003), allowing not only to study the causal role of specific brain areas in behavior, but also, when and how one area affects the activity in other areas (Taylor et al. 2007a, b).

When combined with EEG recordings, TMS offers the opportunity to modify and assess in real time the neural dynamics of widely distributed networks engaged in performing different tasks or learning new skills. EEG allows identifying the local and global brain activities associated with behavioral manifestations of task execution or learning, and TMS can be used to modify these activities to link neuronal with behavioral changes.

As reported in the previous section, active interactions between distant cortical areas have been shown to vary with the functional state of the brain (Massimini et al. 2005). In the motor system, an increase in MEP-amplitude can be achieved by voluntary contraction of the target muscle (Rothwell et al. 1987). Similarly, cortical connections have been shown to be 'modulated' by the system state. Ferbert et al. (1992) showed that the excitability of the transcallosal connections between motor cortices changed depending on whether the subject contracted one or both hands. These findings suggest that TMS effects are sensitive to changes in the cortical state and open the intriguing possibility that administration of TMS-EEG while a subject performs a behavioral task may permit targeting and highlighting specific circuitries.

The work by Morishima et al. (2009) followed exactly this logic. They used TMS as a probe to evaluate the neural impulse transmission from the prefrontal cortex to posterior regions. It is believed that an attentional network exists where top-down signals from the prefrontal cortex modulate the neural processing in the posterior cortices according to behavioral goals (Corbetta and Shulman 2002; Desimone and Duncan 1995). Morishima et al. (2009) hypothesized that stimulation of prefrontal areas of the attentional network would induce a current spread toward the anatomically connected posterior regions, and that the direction and the amount of the current spread could be modulated depending on the functional status of the neural network, the latter set by the task performed by the subjects. During cued attention to visual feature, TMS of the frontal eye field induced activity in different posterior visual areas depending on the nature of the visual feature (Morishima et al. 2009). Moreover, the TMS-EEG approach of effective connectivity used by Morishima et al. (2009) also provided information about the interplay between the prefrontal and posterior areas. TMS effects occurred 20–40 ms after the pulse, suggesting that it was not due to rerouting via other areas, but that there was a direct cortico-cortical signal transmission from frontal to posterior regions.

This illustrates the importance of the interactive approach in the application of the TMS-EEG co-registration. The approach yields real-time measures of whole-brain activity changes while subjects are performing a task and specific areas of the network are concurrently stimulated (real connectivity).

5.4.3 Rhythmic Approach: Connectivity and EEG Frequencies

Combining EEG with TMS can also be used to evaluate changes to brain oscillations in specific frequency bands in a specific area or in the entire brain.

Electrical brain activity consists of distinct patterns of oscillations associated with different perceptual, motor, and cognitive processes (Buzsàki 2006). TMS is expected to change such oscillatory patterns in the directly stimulated cortical area as well as in distant areas belonging to the same neural network. In this respect, the rhythmic approach refers to the possibility of investigating how TMS interacts with oscillatory brain activity (Thut and Miniussi 2009).

A few studies have evaluated the after-effects of repetitive TMS (rTMS) over the motor cortices (Oliviero et al. 2003; Strens et al. 2002). Stimulation of the left motor area at low TMS frequency induced an increase in ipsilateral coherence and in interhemispheric coherence between motor areas in the alpha band (Strens et al. 2002), whereas stimulation at high TMS frequency induced opposite results (Oliviero et al. 2003). These changes may be explained by differential effects on neuronal circuitry linked to inhibitory versus facilitatory processes depending on the stimulation frequency (low- vs. high-frequency rTMS). This would be in line with the idea that low frequency ($\leq$1 Hz) stimulation generally results in inhibition, whereas high frequency ($\geq$5 Hz) stimulation mainly results in excitatory changes in the stimulated area (Chen et al. 1997; Maeda et al. 2000). Nevertheless, it has also been shown that stimulating at different frequencies (1 vs. 20 Hz) over the resting motor cortex (Brignani et al. 2008; Veniero et al. 2011) can induce a power increase in the alpha band, as illustrated in Fig. 5.2. Considering the state of the cortex, these data suggest that alpha generation may represent an intrinsic induced response to TMS targeting the human resting motor cortex.

Low-frequency TMS to the motor or premotor cortex has been shown to affect alpha-activity over ipsilateral motor and to a lesser extent, over contralateral homologous sites (Chen et al. 2003), congruent with enhanced functional interconnectivity of these regions during a motor task (but see also Jing and Takigawa 2000 for high frequency stimulation of the prefrontal cortex). Plewnia et al. (2008) using a new approach evaluated EEG coherence after synchronous bifocal rTMS. Based on the concept of assembly through associative stimulation (Hebbian learning), they hypothesized that by applying synchronous bifocal rTMS over two areas, it might be possible to induce a topographically selective enhancement of interregional coherence. Trains of high-frequency rTMS were applied to the left primary motor cortex and the visual cortex simultaneously. They found that this approach induced a selective increase of interregional coupling in the alpha and lower beta band on the

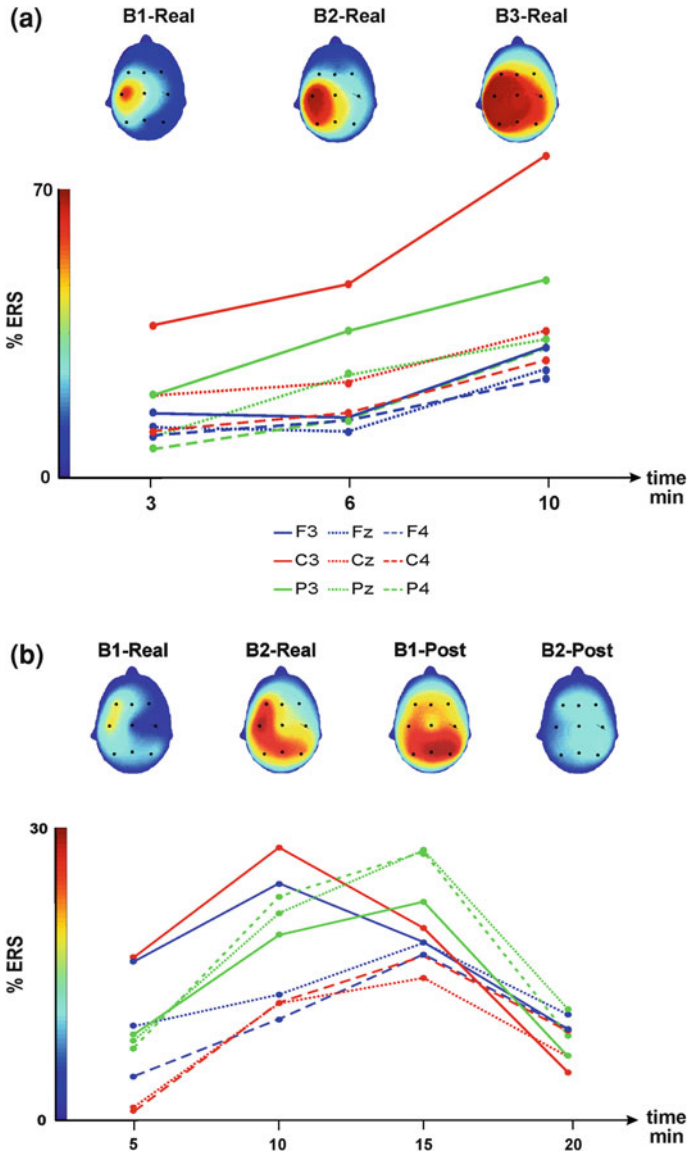

Fig. 5.2 Scalp distribution maps of the event-related power modulations induced by 1 Hz (Panel a) and 20 Hz (Panel b) rTMS for the alpha frequency band using the sham TMS as reference. 1 Hz rTMS data are represented separately for the three successive stimulation blocks (B1, B2, B3 Real) during TMS (Panel A). 20 Hz rTMS data are represented for two successive stimulation blocks (B1, B2 Real) during TMS and two stimulation blocks (B1, B2 Post) after the end of TMS. Voltage is color coded according to the color bar on the left, red color represents maximum relative synchronization. On the x-axis the time of recording in minutes is reported. In the lower part, data are shown for each recording electrode and stimulation block (adapted from Brignani et al. 2008; Veniero et al. 2011)

stimulated sites that lasted up to ten minutes after stimulation (see also Brignani et al. 2008; Veniero et al. 2011). The authors proposed that according to Hebb's rule, enhancement of synaptic efficacy by bifocal simultaneous stimulation may reinforce the connections among cortical areas, as reflected by an increase of oscillatory coupling. It has also been shown that when TMS is tuned to the frequency of the underlying generator (frequency tuned rhythmic TMS), this can entrain on-going brain oscillations in a controlled manner (Thut et al. 2011a) with specific perceptual or behavioral consequences (e.g., reviewed in Thut et al. 2011b). In analogy to Plewnia et al. (2008), it was therefore concluded that rhythmic TMS can be used to generate natural oscillatory signatures.

The rhythmic approach has also been used in a study by Schutter and van Honk (2006) to demonstrate the functional link between cerebellum and frontal areas. Prefrontal and frontal theta activity was observed 200 ms after single-pulse TMS over the cerebellum, therefore, demonstrating a functional connection from the cerebellum to the prefrontal cortex. These results were in line with early animal studies showing cerebellar connectivity to brain structures involved in cognitive and emotional functions (such as the frontal cortices), as well as with studies showing that chronic stimulation of the cerebellum through implanted electrodes normalized the behavior of emotionally dysregulated patients (Heath 1977).

Using a similar rationale, Capotosto et al. (2009) applied TMS over areas known to be involved in the control of visual spatial attention, namely frontal eye-field (FEF) and intraparietal sulcus (IPS), and investigated remote changes in oscillatory activity. Both FEF and IPS stimulation led to a change of the remote regulation of alpha-activity contralateral to attended versus unattended space. This shows that manipulation of activity of an area implied in top-down control leads to a change in oscillations of a downstream network area implied in stimulus processing.

Therefore, this approach offers the possibility to elucidate the relationship between specific oscillatory activity of a network, the interplay between areas and relation to behavior. Moreover, the rhythmic approach can be used to actively generate specific oscillatory signatures and thereby test the functional role of brain rhythms in affective and cognitive functions (for a review see Thut and Miniussi 2009) in connected areas.

5.5 Conclusions

TMS-EEG co-registration offers the unique advantage to simultaneously manipulate and evaluate brain activity and thereby provides valuable information on cortical reactivity and connectivity. The reviewed findings suggest that these measures are highly sensitive to changes in the cortical state, and can be employed to evaluate changes in the connectivity of a given area as a function of different physiological and pathological conditions. Because the brain operates through flexible and interactive distributed networks, we would expect that the modification of a node of the network affects the entire network. If brain stimulation is

applied when the system is in a given functional state, it will bring to evidence the cortico-cortical (or subcortical) network that is effectively connected to the target area at time of TMS, and eventually how that network can be modified by specific tasks, different physiological or pathological states, and pharmacological or behavioral (rehabilitative) treatment approaches.

The significance of concurrent EEG and TMS arises from the possibility to record neuronal responses to the magnetic pulse with a millisecond time scale. This proofs to be a very sensitive method for recording the impact of TMS on the brain and neuronal processes. All in all, this method provides a new way of mapping effective cortical connectivity.

References

Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB (1992) Cerebello-frontal cortical projections in humans studied with the magnetic coil. Electroencephalogr Clin Neurophysiol 85(4):265–272

Bailey CJ, Karhu J, Ilmoniemi RJ (2001) Transcranial magnetic stimulation as a tool for cognitive studies. Scand J Psychol 42(3):297–305

Bender S, Basseler K, Sebastian I, Resch F, Kammer T, Oelkers-Ax R, Weisbrod M (2005) Electroencephalographic response to transcranial magnetic stimulation in children: evidence for giant inhibitory potentials. Ann Neurol 58(1):58–67

Bohning DE, Shastri A, McConnell KA, Nahas Z, Lorberbaum JP, Roberts DR, Teneback C, Vincent DJ, George MS (1999) A combined TMS/fMRI study of intensity-dependent TMS over motor cortex. Biol Psychiatry 45(4):385–394

Bonato C, Miniussi C, Rossini PM (2006) Transcranial magnetic stimulation and cortical evoked potentials: a TMS/EEG co-registration study. Clin Neurophysiol 117(8):1699–1707

Brignani D, Manganotti P, Rossini PM, Miniussi C (2008) Modulation of cortical oscillatory activity during transcranial magnetic stimulation. Hum Brain Mapp 29(5):603–612

Buzsàki G (2006) Rhythms of the brain. Oxford University Press, Oxford

Capotosto P, Babiloni C, Romani GL, Corbetta M (2009) Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. J Neurosci 29(18):5863–5872

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48(5):1398–1403

Chen WH, Mima T, Siebner HR, Oga T, Hara H, Satow T, Begum T, Nagamine T, Shibasaki H (2003) Low-frequency rTMS over lateral premotor cortex induces lasting changes in regional activation and functional coupling of cortical motor areas. Clin Neurophysiol 114(9):1628–1637

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3(3):201–215

Cracco RQ, Amassian VE, Maccabee PJ, Cracco JB (1989) Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. Electroencephalogr Clin Neurophysiol 74(6):417–424

Desimone R, Duncan J (1995) Neural mechanisms of selective visual attention. Annu Rev Neurosci 18:193–222

Esser SK, Huber R, Massimini M, Peterson MJ, Ferrarelli F, Tononi G (2006) A direct demonstration of cortical LTP in humans: a combined TMS/EEG study. Brain Res Bull 69(1):86–94

Ferbert A, Caramia D, Priori A, Bertolasi L, Rothwell JC (1992) Cortical projection to erector spinae muscles in man as assessed by focal transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol 85(6):382–387

Ferrarelli F, Massimini M, Sarasso S, Casali A, Riedner BA, Angelini G, Tononi G, Pearce RA (2010) Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. Proc Natl Acad Sci U S A 107(6):2681–2686

Fregni F, Pascual-Leone A (2007) Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol 3(7):383–393

Fuggetta G, Pavone EF, Walsh V, Kiss M, Eimer M (2006) Cortico-cortical interactions in spatial attention: a combined ERP/TMS study. J Neurophysiol 95(5):3277–3280

Hamidi M, Slagter HA, Tononi G, Postle BR (2010) Brain responses evoked by high-frequency repetitive transcranial magnetic stimulation: an event-related potential study. Brain Stimul 3(1):2–14

Harris JA, Clifford CW, Miniussi C (2008) The functional effect of transcranial magnetic stimulation: signal suppression or neural noise generation? J Cogn Neurosci 20(4):734–740

Heath RG (1977) Modulation of emotion with a brain pacemamer. Treatment for intractable psychiatric illness. J Nerv Ment Dis 165(5):300–317

Hilgetag CC, Theoret H, Pascual-Leone A (2001) Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. Nat Neurosci 4(9):953–957

Hummel FC, Cohen LG (2006) Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 5(8):708–712

Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Naatanen R, Katila T (1997) Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. NeuroReport 8(16):3537–3540

Ipata AE, Girelli M, Miniussi C, Marzi CA (1997) Interhemispheric transfer of visual information in humans: the role of different callosal channels. Arch Ital Biol 135:169–182

Iramina K, Maeno M (2003) Measurement of evoked electroencephalography induced by transcranial magnetic stimulation. J Appl Phys 93(10):6718–6720

Ives JR, Rotenberg A, Poma R, Thut G, Pascual-Leone A (2006) Electroencephalographic recording during transcranial magnetic stimulation in humans and animals. Clin Neurophysiol 117(8):1870–1875

Jing H, Takigawa M (2000) Observation of EEG coherence after repetitive transcranial magnetic stimulation. Clin Neurophysiol 111(9):1620–1631

Julkunen P, Jauhiainen AM, Westeren-Punnonen S, Pirinen E, Soininen H, Kononen M, Paakkonen A, Maatta S, Karhu J (2008a) Navigated TMS combined with EEG in mild cognitive impairment and Alzheimer's disease: a pilot study. J Neurosci Methods 172(2):270–276

Julkunen P, Paakkonen A, Hukkanen T, Kononen M, Tiihonen P, Vanhatalo S, Karhu J (2008b) Efficient reduction of stimulus artefact in TMS-EEG by epithelial short-circuiting by mini-punctures. Clin Neurophysiol 119(2):475–481

Kahkonen S, Kesaniemi M, Nikouline VV, Karhu J, Ollikainen M, Holi M, Ilmoniemi RJ (2001) Ethanol modulates cortical activity: direct evidence with combined TMS and EEG. Neuroimage 14(2):322–328

Komssi S, Kahkonen S (2006) The novelty value of the combined use of electroencephalography and transcranial magnetic stimulation for neuroscience research. Brain Res Rev 52(1):183–192

Komssi S, Aronen HJ, Huttunen J, Kesaniemi M, Soinne L, Nikouline VV, Ollikainen M, Roine RO, Karhu J, Savolainen S et al (2002) Ipsi- and contralateral EEG reactions to transcranial magnetic stimulation. Clin Neurophysiol 113(2):175–184

Komssi S, Kahkonen S, Ilmoniemi RJ (2004) The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation. Hum Brain Mapp 21(3):154–164

Komssi S, Savolainen P, Heiskala J, Kahkonen S (2007) Excitation threshold of the motor cortex estimated with transcranial magnetic stimulation electroencephalography. NeuroReport 18(1):13–16

Litvak V, Komssi S, Scherg M, Hoechstetter K, Classen J, Zaaroor M, Pratt H, Kahkonen S (2007) Artifact correction and source analysis of early electroencephalographic responses evoked by transcranial magnetic stimulation over primary motor cortex. Neuroimage 37(1):56–70

Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A (2000) Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 111(5): 800–805

Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G (2005) Breakdown of cortical effective connectivity during sleep. Science 309(5744):2228–2232

Miniussi C, Rossini PM (2012) Transcranial magnetic stimulation in cognitive rehabilitation. Neuropsychol Rehabil 30:1–23

Miniussi C, Thut G (2010) Combining TMS and EEG offers new prospects in cognitive neuroscience. Brain Topogr 22(4):249–256

Miniussi C, Cappa SF, Cohen LG, Floel A, Fregni F, Nitsche MA, Oliveri M, Pascual-Leone A, Paulus W, Priori A et al (2008) Efficacy of repetitive transcranial magnetic stimulation/transcranial direct current stimulation in cognitive neurorehabilitation. Brain Stimul 1(4):326–336

Miniussi C, Ruzzoli M, Walsh V (2010) The mechanism of transcranial magnetic stimulation in cognition. Cortex 46(1):128–130

Morbidi F, Garulli A, Prattichizzo D, Rizzo C, Manganotti P, Rossi S (2007) Off-line removal of TMS-induced artifacts on human electroencephalography by Kalman filter. J Neurosci Methods 162(1–2):293–302

Morishima Y, Akaishi R, Yamada Y, Okuda J, Toma K, Sakai K (2009) Task-specific signal transmission from prefrontal cortex in visual selective attention. Nat Neurosci 12(1):85–91

Nikulin VV, Kicic D, Kahkonen S, Ilmoniemi RJ (2003) Modulation of electroencephalographic responses to transcranial magnetic stimulation: evidence for changes in cortical excitability related to movement. Eur J Neurosci 18(5):1206–1212

Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, Paulus W, Hummel FC, Boggio PS, Fregni F et al (2008) (2008) Transcranial direct current stimulation: state of the art. Brain Stimul 1(3):206–223

Oliviero A, Strens LH, Di Lazzaro V, Tonali PA, Brown P (2003) Persistent effects of high frequency repetitive TMS on the coupling between motor areas in the human. Exp Brain Res 149(1):107–113

Pascual-Leone A, Dhuna A, Roth BJ, Cohen L, Hallett M (1990) Risk of burns during rapid-rate magnetic stimulation in presence of electrodes. Lancet 336(8724):1195–1196

Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S, Valls-Sole J, Brasil-Neto JP, Wassermann EM, Cohen LG et al (1993) Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electroencephalogr Clin Neurophysiol 89(2):120–130

Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M (1994) Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117(Pt 4):847–858

Plewnia C, Rilk AJ, Soekadar SR, Arfeller C, Huber HS, Sauseng P, Hummel F, Gerloff C (2008) Enhancement of long-range EEG coherence by synchronous bifocal transcranial magnetic stimulation. Eur J Neurosci 27(6):1577–1583

Quartarone A, Bagnato S, Rizzo V, Morgante F, Sant'angelo A, Battaglia F, Messina C, Siebner HR, Girlanda P (2005) Distinct changes in cortical and spinal excitability following high-frequency repetitive TMS to the human motor cortex. Exp Brain Res 161(1):114–124

Ridding MC, Rothwell JC (2007) Is there a future for therapeutic use of transcranial magnetic stimulation? Nat Rev Neurosci 8(7):559–567

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS consensus Group (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120(12):2008–2039

Roth BJ, Pascual-Leone A, Cohen LG, Hallett M (1992) The heating of metal electrodes during rapid-rate magnetic stimulation: a possible safety hazard. Electroencephalogr Clin Neurophysiol 85(2):116–123

Rothwell JC, Day BL, Thompson PD, Dick JP, Marsden CD (1987) Some experiences of techniques for stimulation of the human cerebral motor cortex through the scalp. Neurosurgery 20(1):156–163

Ruzzoli M, Marzi CA, Miniussi C (2010) The neural mechanisms of the effects of transcranial magnetic stimulation on perception. J Neurophysiol 103(6):2982–2989

Sack AT, Linden DE (2003) Combining transcranial magnetic stimulation and functional imaging in cognitive brain research: possibilities and limitations. Brain Res Brain Res Rev 43(1):41–56

Sandrini M, Umilta C, Rusconi E (2010) The use of transcranial magnetic stimulation in cognitive neuroscience: a new synthesis of methodological issues. Neurosci Biobehav Rev 35(3):516–536

Schutter DJ, van Honk J (2006) An electrophysiological link between the cerebellum, cognition and emotion: frontal theta EEG activity to single-pulse cerebellar TMS. Neuroimage 33(4): 1227–1231

Sekiguchi H, Takeuchi S, Kadota H, Kohno Y, Nakajima Y (2011) TMS-induced artifacts on EEG can be reduced by rearrangement of the electrode's lead wire before recording. Clin Neurophysiol 122(5):984–990

Selimbeyoglu A, Parvizi J (2010) Electrical stimulation of the human brain: perceptual and behavioral phenomena reported in the old and new literature. Front Hum Neurosci 4:46

Siebner HR, Bergmann TO, Bestmann S, Johansen-Berg H, Mochizuki H, Bohning DE, Boorman ED, Groppa S, Miniussi C, Pascual-Leone A et al (2009) Consensus paper: combining transcranial stimulation with neuroimaging. Brain Stimul 2(2):58–80

Silvanto J, Cowey A, Lavie N, Walsh V (2005) Striate cortex (V1) activity gates awareness of motion. Nat Neurosci 8(2):143–144

Strens LH, Oliviero A, Bloem BR, Gerschlager W, Rothwell JC, Brown P (2002) The effects of subthreshold 1 Hz repetitive TMS on cortico-cortical and interhemispheric coherence. Clin Neurophysiol 113(8):1279–1285

Taylor PC, Nobre AC, Rushworth MF (2007a) FEF TMS affects visual cortical activity. Cereb Cortex 17(2):391–399

Taylor PC, Nobre AC, Rushworth MF (2007b) Subsecond changes in top down control exerted by human medial frontal cortex during conflict and action selection: a combined transcranial magnetic stimulation electroencephalography study. J Neurosci 27(42):11343–11353

Taylor PC, Walsh V, Eimer M (2008) Combining TMS and EEG to study cognitive function and cortico-cortico interactions. Behav Brain Res 191(2):141–147

Taylor PC, Walsh V, Eimer M (2010) The neural signature of phosphene perception. Hum Brain Mapp 31(9):1408–1417

Thut G, Miniussi C (2009) New insights into rhythmic brain activity from TMS-EEG studies. Trends Cogn Sci 13(4):182–189

Thut G, Northoff G, Ives JR, Kamitani Y, Pfennig A, Kampmann F, Schomer DL, Pascual-Leone A (2003) Effects of single-pulse transcranial magnetic stimulation (TMS) on functional brain activity: a combined event-related TMS and evoked potential study. Clin Neurophysiol 114(11):2071–2080

Thut G, Nietzel A, Pascual-Leone A (2005) Dorsal posterior parietal rTMS affects voluntary orienting of visuospatial attention. Cereb Cortex 15(5):628–638

Thut G, Schyns PG, Gross J (2011a) Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. Front Psychol 2:170

Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J (2011b) Rhythmic TMS causes local entrainment of natural oscillatory signatures. Curr Biol 21(14):1176–1185

Valero-Cabre A, Pascual-Leone A (2005) Impact of TMS on the primary motor cortex and associated spinal systems. IEEE Eng Med Biol Mag 24(1):29–35

Valero-Cabre A, Rushmore RJ, Payne BR (2006) Low frequency transcranial magnetic stimulation on the posterior parietal cortex induces visuotopically specific neglect-like syndrome. Exp Brain Res 172(1):14–21

Veniero D, Bortoletto M, Miniussi C (2009) TMS-EEG co-registration: on TMS-induced artifact. Clin Neurophysiol 120(7):1392–1399

Veniero D, Maioli C, Miniussi C (2010) Potentiation of short-latency cortical responses by high-frequency repetitive transcranial magnetic stimulation. J Neurophysiol 104(3):1578–1588

Veniero D, Brignani D, Thut G, Miniussi C (2011) Alpha-generation as basic response-signature to transcranial magnetic stimulation (TMS) targeting the human resting motor cortex: A TMS/EEG co-registration study. Psychophysiology. doi:10.1111/j.1469-8986.2011.01218.x

Virtanen J, Ruohonen J, Naatanen R, Ilmoniemi RJ (1999) Instrumentation for the measurement of electric brain responses to transcranial magnetic stimulation. Med Biol Eng Comput 37(3):322–326

Walsh V, Cowey A (2000) Transcranial magnetic stimulation and cognitive neuroscience. Nat Rev Neurosci 1(1):73–79

Wassermann EM, Epstein C, Ziemann U, Walsh V, Paus T, Lisanby S (2008) Handbook of tanscranial stimulation. Oxford University press, Oxford, UK

Zanon M, Busan P, Monti F, Pizzolato G, Battaglini PP (2010) Cortical connections between dorsal and ventral visual streams in humans: evidence by TMS/EEG co-registration. Brain Topogr 22(4):307–317

Chapter 6
Interactions Between Cortical Areas During Skilled Grasp and Modulation by Brain Stimulation

Cortico-Cortical Interactions During Grasp

Marco Davare

Abstract The hand is the principal organ through which we interact with our environment. Skilled grasp is a sensorimotor process requiring the brain to transform sensory information into a precise motor command. In the past decade, functional neuroimaging has proved extremely useful in mapping the human motor circuits involved in skilled hand movements. However, one major drawback of this approach is that it could not determine the exact contribution of each individual cortical area to precision grasping. Transcranial magnetic stimulation (TMS) can be used to induce transient 'virtual lesions' of discrete brain areas in healthy subjects while performing a motor task. As such, it is the only technique in humans to probe whether a specific area is causally responsible for controlling the motor task under investigation. Recent TMS studies have allowed us to determine the specific contribution of distinct parietal and frontal areas to the control of both the kinematics and dynamics of precision grasping. Moreover, although a large body of the literature has focused on which brain areas either integrate the visual object's properties or control the motor output, it is still unclear how grasp-related information is transferred from one area to another. Understanding of the interactions between brain areas is crucial for the study of visuomotor transformations. Recently, new advances have shown it is possible to study corticocortical interactions during different task contexts. This sheds new light on how brain areas are integrated in a dynamic network for controlling grasping actions.

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6.1 Introduction

The special relationship we indubitably enjoy with the material universe is to a very great extent the result of the special virtues of our hands (Tallis 2003). Fine manipulative skills and precise tool use are a unique attribute of the human species. Although some non-human primates are also able to perform sophisticated hand movements, including the use of simple tools, the human manipulative superiority arises most likely from the intimate interactions between motor skills and higher cognitive functions. Skilled hand functions contribute to several aspects of our daily life and are crucial for our technology, communication, culture and social interaction. The loss of hand function is devastating. In a survey of quadriplegic patients, the regaining of arm and hand function was ranked as most important (Anderson 2004).

Reaching out and grasping an object requires the processing of its precise location with respect to our hand and the integration of the object's intrinsic properties such as its size and shape (Jeannerod et al. 1995; Castiello 2005). These visual attributes have then to be transformed into an appropriate motor command that will guide and shape our hand for efficient grasp of the object. In addition, internal models related to object weight are learnt through previous motor experience and allow prediction of the actual fingertip forces required for lifting the object (Flanagan and Wing 1997; Witney et al. 2000; Wolpert and Flanagan 2001; Johansson and Flanagan 2009).

In the past decade, functional neuroimaging studies have reopened several major questions in human motor neuroscience. One important issue is the neural correlates of skilled hand movements and, particularly, of precision grasping. Neuroimaging studies have shown that, in addition to the corticospinal system (Lemon et al. 1995; Lemon 2008), precision grasping critically relies on an extensive cortical network, including the dorsal (PMd) and ventral (PMv) premotor cortex and the supplementary motor area (SMA) and a mosaic of areas located in the intraparietal sulcus (IPS) (Binkofski et al. 1999; Ehrsson et al. 2000, 2001, 2003; Cavina-Pratesi et al. 2007, 2010). When using tools or manufactured objects, the activated areas extend to the convexity of the inferior parietal lobule (Chao and Martin 2000; Johnson-Frey et al. 2005; Culham and Valyear 2006). Although it is sensible to assume that each motor-related area has a specific contribution to precision grasping, neither functional imaging studies nor clinical studies have allowed us to answer this question definitely. Transcranial magnetic stimulation (TMS) can be used to induce transient 'virtual lesions' of discrete brain areas in healthy subjects while performing a motor task (Sack 2006). As such, it is the only technique in humans to probe whether a specific area is causally responsible for controlling the motor task under investigation. Several recent TMS studies have allowed us to determine how different parietal and frontal areas contribute to the visuomotor transformations underlying skilled grasp.

The second important issue is the functional connectivity between areas of the 'cortical grasping circuit' (Grafton 2010; Davare et al. 2011). A better understanding of

functional interactions taking place in this cortical circuit will shed light on how sensory information about the object properties is conveyed to the motor cortex and transformed into a motor command. Recent studies provide new insights about how grasp-related information is transferred between the parietofrontal network and the primary motor cortex (M1) (Koch et al. 2006, 2007, 2008, 2010; Davare et al. 2008, 2009, 2010, 2011; Baumer et al. 2009). Finally, new findings suggest interactions between the object recognition system in the 'ventral' occipito-temporal stream and the system controlling goal-directed actions in the 'dorsal' occipito-parietal stream (Verhagen et al. 2008; Cohen et al. 2009). It has been found that areas in the ventral stream are involved in the control of delayed grasping (based on a memory of the object). This suggests that while the dorsal stream may be sufficient to control the grasp online, after a delay, information about the object's intrinsic properties may be recruited from ventral stream areas to control the grasp (Cohen et al. 2009). Ventral-to-dorsal stream interactions could be important as a means of sharing the details of an object's properties in order to fine-tune the motor command for grasping it.

The present chapter offers an overview of recent studies which have shed light on the neural correlates of skilled grasp and on the functional connectivity between areas of the cortical grasping network.

6.2 Neural Correlates of Hand Shaping

When reaching for an object, one crucial step is to shape the hand according to an object's size, geometry, and orientation (Goodale et al. 1994; Jeannerod et al. 1995). Electrophysiological studies in monkeys (Murata et al. 1997, 2000; Raos et al. 2006; Umilta et al. 2007) and functional neuroimaging studies in humans (Binkofski et al. 1999; Frey et al. 2005; Begliomini et al. 2007; Grol et al. 2007; Cavina-Pratesi et al. 2010) have shown that a cortical circuit consisting of the anterior part of the IPS (AIP) connected to PMv is responsible for processing visuospatial information about the object (Castiello 2005; Raos et al. 2006). However, the exact contribution of AIP and PMv is still unclear and reversible inactivation of these two areas in monkeys has failed to differentiate their role in precision grasping (Gallese et al. 1994; Fogassi et al. 2001). Moreover, it is noteworthy that recent evidence has questioned the existence of such a dorsolateral 'grasping circuit' purely dedicated to grasping movements (Grol et al. 2007; Fattori et al. 2010).

Two recent TMS studies have investigated the role of AIP and PMv in humans (Davare et al. 2006, 2007) by inducing a transient virtual lesion of either area in healthy subjects performing a standard grip–lift task (Fig. 6.1). With the hand laid relaxed on its ulnar edge and the thumb and index finger positioned 4 cm apart from the manipulandum grip surfaces, subjects were instructed to grip the manipulandum and to lift it by applying the minimum force required to avoid slips (Johansson and Westling 1984). An auditory GO signal was delivered at the beginning of the trial. Virtual lesions were induced by using repetitive TMS

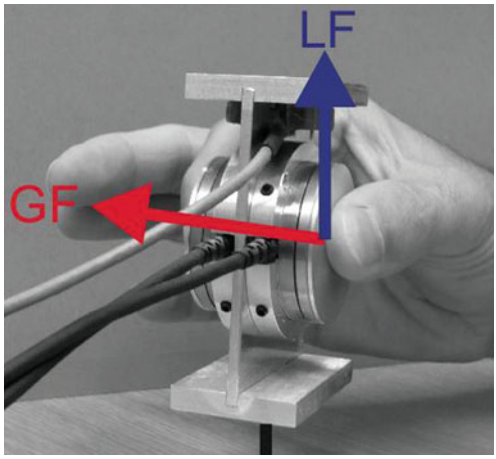


Fig. 6.1 Manipulandum used for the grip–lift task. Subjects had to lift the manipulandum between the thumb and index finger, by applying the minimum force required to prevent slipping. The manipulandum contained two three-dimensional force–torque sensors that allow measuring the grip force (GF) and load force (LF) developed at each fingertip, and the fingertip contact positions on the graspable 4 cm diameter surface

(10 Hz, 5 pulses, 120 % of resting motor threshold [rMT]) triggered on the GO signal. We showed that a bilateral lesion of AIP was necessary to alter the finger positioning of either hand (Fig. 6.2d–e), suggesting that, in humans, both AIP contribute critically to hand shaping, irrespective of the hand used (Davare et al. 2007). This finding is compatible with neuroimaging studies showing a bilateral recruitment of AIP in tasks requiring unimanual movements (Binkofski et al. 1999; Ehrsson et al. 2000, 2001; Culham et al. 2003; Castiello 2005; Culham and Valyear 2006), as already suggested by monkey experiments (Sakata et al. 1995). Other recent TMS studies have also highlighted the role of AIP in controlling the hand shaping 'online', when an error was detected during the hand transport, for example when the object size or orientation was unexpectedly changed after movement initiation (Glover et al. 2005; Tunik et al. 2005; Rice et al. 2006). This indicates that AIP is not only involved in planning the hand shaping during movement preparation, but has also a key role for online adjustments of the grasp that are goal-dependent (Tunik et al. 2005; Rice et al. 2006).

In contrast to AIP, a unilateral lesion of either PMv was found sufficient to impair selectively the shaping of the right dominant hand (Fig. 6.2a–c), indicating that both PMv are necessary to perform visuomotor transformation of intrinsic features of the object (Jeannerod et al. 1995; Castiello 2005), a finding consistent with neuroimaging studies demonstrating a bilateral activation in both PMv when subjects manipulate (Binkofski et al. 1999) or grasp an object (Ehrsson et al. 2000; 2001). Besides its contribution to hand shaping, PMv was also found to influence the timing of the intrinsic hand muscle recruitment. However, we found that only lesions of the left PMv altered the recruitment of intrinsic muscles of the right hand, in accordance with monkey experiments showing that an inactivation of PMv influences the timing of the agonist–antagonist muscle recruitment in the contralateral hand (Matsumura et al. 1991). These results suggest that, at an early stage of the movement preparation, both PMv are involved in the visuomotor transformations leading to the appropriate hand shaping and that, once a given

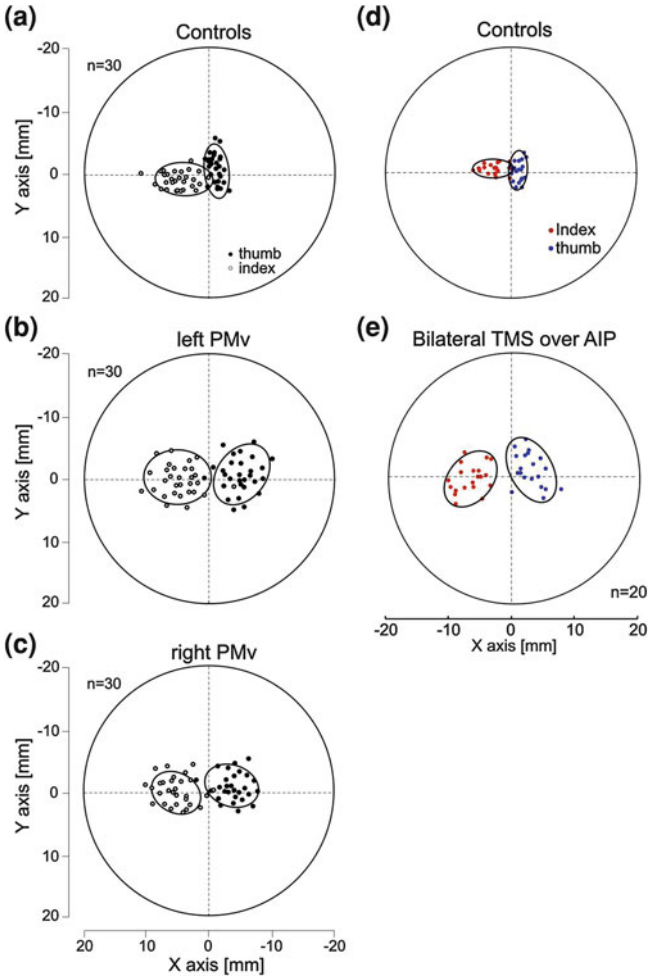


Fig. 6.2 Effect of TMS on the fingertip positioning. Side view of the manipulandum showing the distribution of the fingertip positions for the thumb (*black or blue circles*) and the index finger (*white or red circles*). The two graspable surfaces of the manipulandum were superimposed to represent the thumb and index fingertip positions on the same graph. The subject's hand came from the right side of the figure. The ellipses represent the area in which 95 % of the fingertip positions were found. **a** distribution of the thumb and index fingertip positions for 30 control trials in one subject. Note that, the index finger contact points were always slightly further than those of the thumb. **b** *left* PMv TMS increased significantly both the horizontal distance between the thumb and index finger contact points and their variability. **c** similar effects, although less pronounced, of *right* PMv TMS. **d** control condition for AIP virtual lesions. **e** effect of a *bilateral* AIP TMS on finger positioning which led to a larger dispersion of fingertip positions on the manipulandum

hand is selected to perform the movement, only the contralateral PMv is involved in implementing the grasp motor command.

In summary, it is reasonable to assume that AIP feeds PMv with visual information about an object's intrinsic properties, whereas PMv implements the motor aspect of the grasp component. Recurrent feedback loops between PMv and AIP allow further computation of any mismatch between the grasp conformation and the object intrinsic properties if a change in object orientation occurs (Raos et al. 2006). This view is compatible with the high connection probability found between PMv and AIP in humans (Tomassini et al. 2007) and with the fact that grasping small objects led to an increase in the effective connectivity between these two areas, probably because fine movements highly rely on online control (Grol et al. 2007).

Finally, to determine more precisely the time course of the contribution of AIP and PMv in the grip–lift task, we used paired-pulse TMS (5 ms interval, both pulses at 120 % rMT) applied over PMv or AIP at five different delays after the Go signal (50–250 or 0–200 for PMv and AIP, respectively). We showed that during movement preparation, the contribution of AIP to hand shaping occurs about 50 ms before that of PMv, supporting the classical view that AIP and PMv interact serially at an early stage of movement preparation (Jeannerod et al. 1995; Castiello 2005).

6.3 Neural Correlates of Grip Force Control

Another critical parameter that has to be controlled once the fingers made contact with the object is the development of fingertip force. The so-called grip force has to be precisely scaled in order to prevent the object from slipping or from being damaged (Johansson and Westling 1988). Scaling the grip force according to the weight and frictional properties of the objects is programmed anticipatorily, an ability thought to rely on internal models (Flanagan and Wing 1997). Studies in brain damaged patients indicate that lesions encompassing parts of the occipital and parietal lobes alter the ability to anticipate the grip forces correctly (Nowak et al. 2003) and patients with cerebellar lesions apply too high grip force, revealing a strategy to compensate for their inappropriate grip force anticipation (Nowak et al. 2002). These observations suggest that both the parietal cortex and cerebellum are critically involved in the implementation and the storage of the object's internal models. Neuroimaging studies have shown that both the cerebellum and the SMA are involved in the grip force adjustment when the object weight changes unpredictably (Bursztyn et al. 2006; Jenmalm et al. 2006), whereas intraparietal areas are rather involved in monitoring the difference between the predicted and the actual object weight, without implementing the corrective motor command (Jenmalm et al. 2006).

In particular, it has been shown that virtual lesions of AIP led to an increase in grip force (Davare et al. 2007) (Fig. 6.3), suggesting that the subjects

overestimated the weight of the object, exactly as reported in experiments in which the object is unexpectedly replaced by a lighter one (Johansson and Westling 1988). Interestingly, only a virtual lesion of the left, but not right, AIP produced such an effect. Therefore, it is logical to assume that the left AIP is involved in the implementation—or the retrieval—of object internal models (Flanagan and Wing 1997). Additionally, using the paired-pulse TMS paradigm described above, it has been shown that this process is performed by AIP about 150 ms before the fingers contact the object (Davare et al. 2007), namely 100 ms after AIP processed hand shaping. This corroborates the view of Jenmalm and colleagues (2006) that IPS areas monitor the mismatch between the anticipated and actual object weight in order to update the internal model and, if required, to trigger a correction (Jenmalm et al. 2006). In another study (Dafotakis et al. 2008), single pulse TMS was delivered either over AIP or PMv at two different time points of the grasping movement (movement onset or time of peak grasp aperture) while subjects had to lift objects of two different weights, in random order. Dafotakis et al. found that PMv had a causal role in predicting grip force when a sensorimotor memory from the previous lift is used. Moreover, delivering TMS over AIP affected reactive adjustments, but not prediction, of the grip force (Dafotakis et al. 2008), which is in line with the view that AIP is involved in implementing motor corrections if there is a mismatch between the predicted and the actual object weight (Jenmalm et al. 2006). Finally, whereas PMv TMS effects were only observed at the late time point, AIP TMS effects were found for both the early and late time points. The sequential involvement of AIP and PMv in planning or adjusting grip forces (Dafotakis et al. 2008) parallels the time course of AIP and PMv in controlling hand shaping (Davare et al. 2006; 2007). Although interesting, further experiments are still required to investigate whether AIP and PMv encode digit positioning and force development in parallel.

As far as the timing of fingertip force development is concerned, we found that left PMd virtual lesions delayed the recruitment of proximal muscles involved in object lifting, leading to a late generation of the load force, and therefore to less synchronised grip and lift movements (Davare et al. 2006). This suggests that PMd may control the correct timing of the lifting phase with respect to the grasping phase. It is known that PMd is involved in movement preparation when hand movements are conditioned to either external cues (Schluter et al. 1998; Chouinard et al. 2005) or internal cues, as in complex sequences of finger tapping (Haaland et al. 2004). Because the lifting phase can only be initiated when finger positioning is completed and when the grip force has reached an adequate level, our results are compatible with a role of PMd in initiating the lifting phase, however, more likely based on somatosensory signals than on visual or arbitrary cues (Johansson and Westling 1984). Interestingly, our TMS studies (Davare et al. 2006; 2007) demonstrate that the left hemispheric dominance not only concerns high-level processes such as hand–tool interactions (De Renzi et al. 1980; Koski et al. 2002; Culham and Valyear 2006; Daprati and Sirigu 2006), but also applies to more elementary aspects of movements, such as the encoding of force when lifting an object.

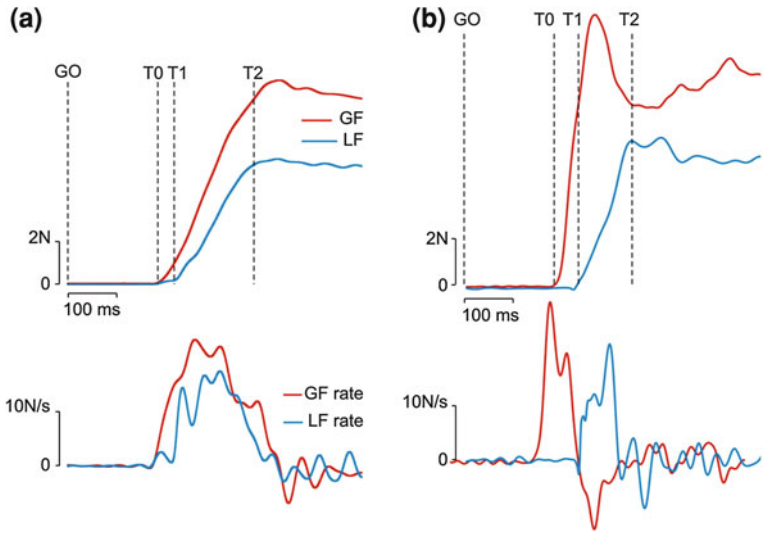


Fig. 6.3 Fingertip force recordings. **a** typical recording of fingertip forces in control conditions illustrating the grip–lift synergy. Grip force (GF) is in *red*, lift force (LF) is in *blue*, and, shown below is their first derivatives (same colour code). T0–T1, Preloading phase; T1–T2, loading phases. **b** effect of left AIP virtual lesions. Both GF and GF rate overshot control values and the preloading phase (T0–T1) increased significantly

6.4 What is Represented in the Different Components of the Visuomotor Cortical Network for Skilled Grasp?

The classical model of the neural control of reaching and grasping movements proposes that areas located in the antero-lateral portion of the IPS integrate grasp-related information about an object whereas a more postero-medial region of the IPS contributes to the planning of reaching movements towards the object. AIP contains visual and visuomotor neurons that are activated by a particular type of grasp (Sakata et al. 1995; Murata et al. 2000), while the medial IPS and area V6A contain neurons associated with a particular direction of reach (Andersen and Buneo 2002).

All these structures feature in modern views of the reach and grasp network (Fig. 6.4; Grafton (2010)). In order to show grasp-related selectivity of neurons in many component areas of the network, it has been necessary to test a wide range of grasps (Murata et al 2000; Brochier et al. 2004; Umilta et al. 2007). This approach first demonstrated that area F5, the rostral part of the ventral premotor cortex (PMv) in the macaque monkey, contains visuomotor and motor neurons which are selectively active while the animal is fixating and grasping objects of a particular shape using a particular range of grasps (Murata et al. 1997; Raos et al. 2006; Umilta et al. 2007). This kind of detailed study led to the concept of 'canonical'

neurons in area F5 which are thought to form a motor repertoire of possible grasping actions (Rizzolatti and Luppino 2001). Some recent findings challenge the view that the reach and grasp components are processed independently. Fattori et al. (2010) have recently reported neurons in V6A whose activity is modulated by grasp type, and where the influence of visual inputs, reach activity and wrist orientation could be excluded (Fattori et al. 2009, 2010). Thus, although the classical view suggests that neurons in this area encode the direction of the arm towards different spatial locations, these recent findings suggest that area V6A may be involved in controlling both the reach and the grasp. There is also evidence of grasp-specific activity from recordings in the dorsal premotor cortex (PMd/F2) (Raos et al. 2004; Stark et al. 2007), even though this is traditionally part of the dorsomedial reach-dominated network. Moreover, a grasp-specific representation within PMd is predicted by its neuroanatomical connectivity, with heavy interactions with digit representations in both PMv (F5) and M1 (Dum and Strick 2005; Boudrias et al. 2010).

Of course, biomechanical constraints mean that the execution of a particular type of grasp will be influenced by the position and orientation of the object in the workspace, and it is of interest to know whether 'grasp-related' activity in classically grasp-dominated areas is in fact influenced by object orientation. In recent papers, it was shown that wrist orientation can strongly influence grasp-related activity in both AIP (Baumann et al. 2009) and F5 (Fluet et al. 2010). Moreover, using TMS in humans, it has been found that the corticospinal excitability of particular hand muscles is modulated by the shoulder position, suggesting a flexible cortical drive to hand muscles depending on arm position (Dominici et al. 2005). In a task where the grip force has to be kept constant, the drive to both intrinsic and extrinsic hand muscles is modulated by wrist orientation (Johnston et al. 2010). Therefore, even if only the force generated by extrinsic hand muscles is influenced by different wrist angles, it seems that the motor system controls both intrinsic and extrinsic hand muscles as a synergistic group. Extending this notion raises the idea that commands related to the transport component, and involving proximal muscles, also influence the activity of distal muscles required for the grasp.

In humans, functional imaging studies also show evidence that the control of the reach and grasp components might not be independent. It has been found that areas in the dorsomedial pathway (V6A and PMd) were strongly coupled during grasping, in a similar fashion to the coupling of AIP and PMv in the dorsolateral circuit (Grol et al. 2007). Interestingly, AIP and PMv were more coupled during grasp of a small object (Grol et al. 2007). In addition, the AIP–PMv circuit showed strong coupling with the lateral occipital complex (LOC) in conditions where perceptual information about an object was critical to achieve an appropriate grasp (Verhagen et al. 2008). This suggests that the AIP–PMv circuit could incorporate physical details originating from the ventral visual stream to fine-tune the grasp.

To sum up, it would appear that the control of grasp relies on both the dorsomedial and dorsolateral pathways. However, AIP seems to have a particular

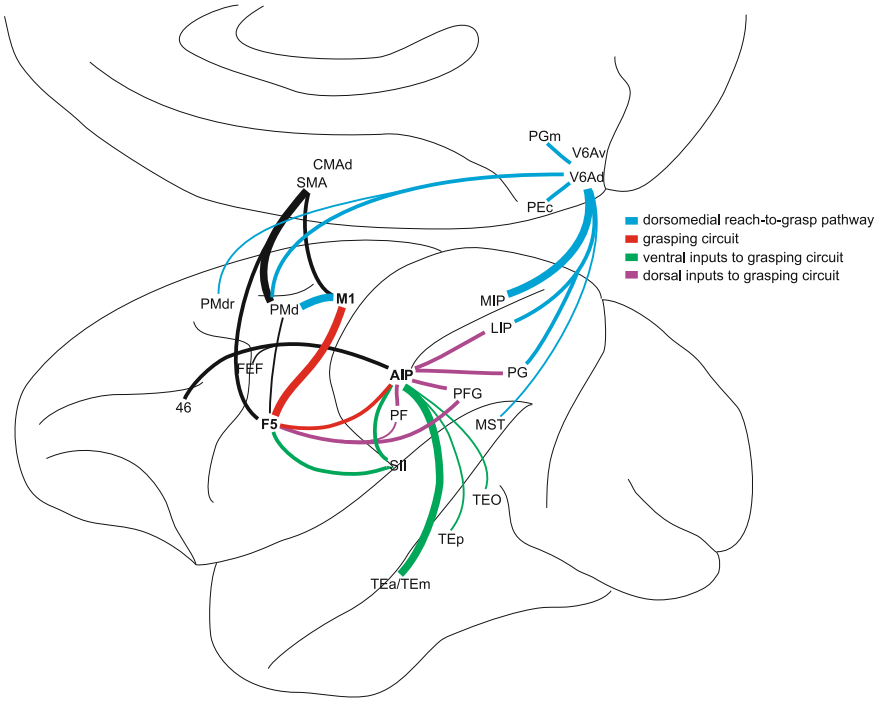


Fig. 6.4 Anatomical connections of the cortical grasping network based on tract tracing in non-human primates (adapted from Grafton 2010). Anatomical labelling is approximate. The anterior intraparietal area (AIP) is a key node for processing grasp-related object properties. AIP is part of the dorsolateral 'grasping' circuit (in *red*). It receives inputs from areas located in the dorsal stream (inferior parietal lobule [PF, PFG, PG] and the lateral intraparietal area [LIP], in *purple*) and from areas in the ventral stream (secondary somatosensory cortex [SII], infero-temporal [TEa/TEm, TEp, TEo] and medio-superior temporal lobule [MST], in *green*). These inputs provide AIP with real-time details about an object's properties together with stored knowledge about its identity. AIP makes reciprocal connections with ventral premotor area (PMv/F5) that in turn is reciprocally connected to the primary motor cortex (M1) hand area. These AIP–F5–M1 interactions are grasp-specific and crucial for controlling visually guided grasp. The dorsomedial 'reach-to-grasp' circuit (in *blue*) involves area V6A. It is connected with the medial intraparietal area (MIP), LIP, PG, MST, mesial parietal areas (PEc and PGm) and the dorsal premotor cortex (PMd, PMdr)

functional specialisation for grasp that is dependent on online visuomotor control. PMd may be more concerned in coupling the grasp to other aspects of the movement, such as reaching for the object (Cavina-Pratesi et al. 2010) or lifting it after it has been grasped (Davare et al. 2006). Such a role could be supported by the presence within PMd of both distal and proximal arm muscle representations (Dum and Strick 2005; Boudrias et al. 2010).

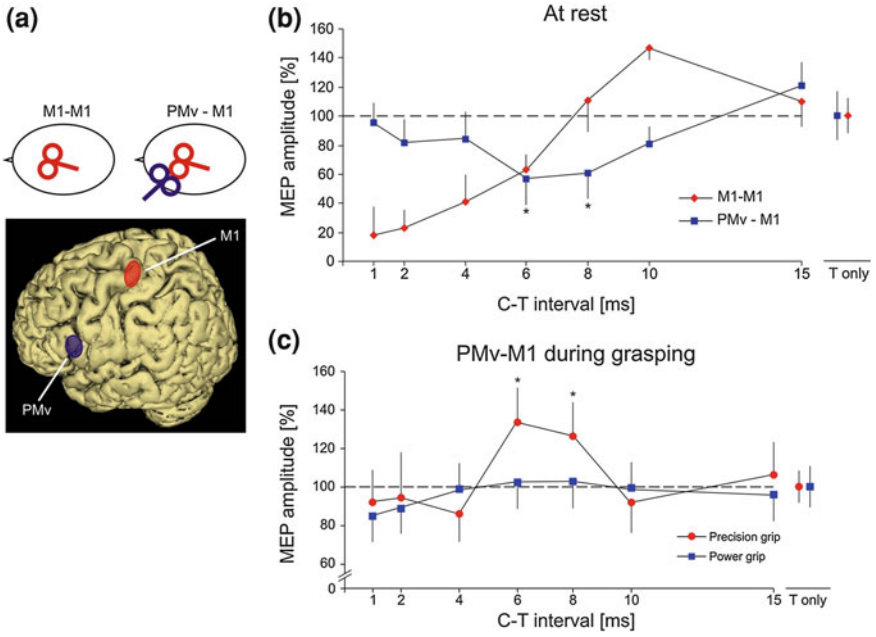


Fig. 6.5 **a** TMS sites in the double-coil TMS paradigm. Schematic view of the coil positions in the M1–M1 and the PMv–M1 conditions. Location of the TMS sites as given by the neuronavigation: PMv is shown in *blue* (mean MNI coordinates: −58, 13, 19), M1 in *red* (mean coordinates: −38, −23, 60). The ellipses illustrate the 95 % confidence interval centred over the mean calculated for all subjects (n = 7). **b** PMv–M1 interactions at rest. Relative amplitude of MEPs recorded from the first dorsal interosseous (1DI) muscle at rest. The *blue squares* (PMv–M1 condition) represent MEP amplitudes resulting from a suprathreshold test (T) stimulus applied over M1 preceded by a subthreshold conditioning (C) stimulus applied over PMv at different intervals (X-axis). A significant suppression was found at both the 6 and 8 ms C–T intervals. *Red diamonds* show MEP amplitude recorded during the M1–M1 condition. The error bars show 1 S.D. **c** PMv–M1 interactions during grasp. Relative amplitude of MEPs recorded from the 1DI during a 10 % maximum voluntary contraction either during a precision grip (*red*) or a power grip (*blue*). During a precision grip, the resting PMv–M1 inhibition turned into facilitation at both the 6 and 8 ms C–T intervals, whereas, during a power grip this inhibition was cancelled

6.5 Transfer of Grasp-Related Information Between Areas of the Cortical Grasping Circuit

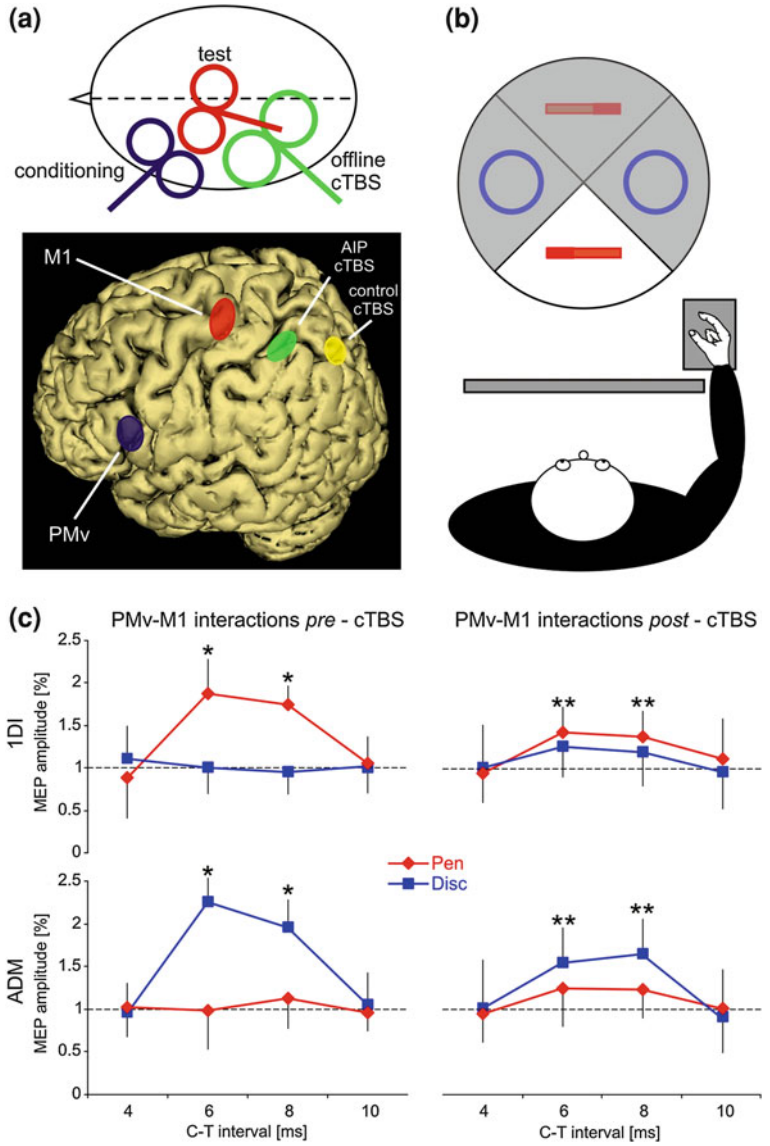
The characteristic properties of a given component of the cortical network are not intrinsic to that area but arise from its specific connections with other members of the network. Because of their particular role in controlling grasping movements, the interactions between AIP, PMv and M1 have been the subject of recent intensive research. AIP and PMv are reciprocally connected and receive inputs from the ventral visual stream areas, including the lower bank of the superior

Fig. 6.6 **a** Coil orientations and location of the TMS sites as given by neuronavigation; the ventral premotor (PMv) (−56, 13, 18) is shown in *blue*, the primary motor cortex (M1) (−34, −25, 57) in *red*, the anterior intraparietal area (AIP) (−43, −39, 46) in green, and the control theta-burst TMS (cTBS) site in *yellow* (n = 9). **b** Experimental task: subjects had to grasp objects at their own pace using either a precision grip between the index and thumb or a whole-hand grasp. A turntable randomly presented the objects 30 cm in front of the subject's hand pad. A screen, made from switchable transparent glass, was positioned between the subject and the turntable to allow precise timing of object presentation. **c** Effect of AIP cTBS on PMv–M1 interactions. Relative amplitude of motor-evoked potentials (MEPs) recorded from the 1DI and abductor digiti minimi (ADM) muscles when preparing to grasp either the pen or the disc (*left*: before cTBS; *right*: after cTBS). Y-axis values represent the relative MEP amplitudes resulting from a suprathreshold test (T) stimulus applied over M1 preceded by a subthreshold conditioning (C) stimulus applied over PMv at different C–T intervals (x-axis). Note that, the facilitation of the 1DI when grasping the pen and of the ADM when grasping the disc ($*p < 0.05$) decreased following cTBS ($**p < 0.05$) ▶

temporal sulcus in the region of areas TEa/TEm and the middle temporal gyrus (Borra et al. 2008), and the second somatosensory area (SII). Rapid access by the AIP–PMv circuit to object identity information stored in the ventral stream could be critical to fine-tune the grasp, so that it is appropriate for a particular object.

Previous sections in this chapter have concluded that PMv has a pivotal role in controlling hand shaping. However, it is still unclear how information about the grasp processed in PMv gives rise to appropriate motor commands for transmission to spinal motoneurones innervating hand muscles. Although the role of PMv in precision grasping is well established, in monkeys this cortical area surprisingly sends relatively few direct projections to the cervical enlargement (Dum and Strick 1991; He et al. 1993; Dum and Strick 2005). Therefore, it has been suggested that PMv contributes to the control of hand shaping through its corticocortical connections with M1 (Cerri et al. 2003; Shimazu et al. 2004). This view has been corroborated by the finding that, in monkeys, F5 stimulation facilitates descending corticospinal volleys from M1, an effect that is abolished by reversible inactivation of M1 (Shimazu et al. 2004). Finally, it is well known that intracortical stimulation of F5 evokes characteristic digit movements; these movements are also abolished by reversible inactivation of M1 (Schmidlin et al. 2008).

In humans, little is known about the nature of PMv–M1 connections at rest and about the possible modulation of these interactions during different types of grasp (prevision grip vs power grip). In the first study, we used TMS in a double-coil protocol to address this issue: TMS was applied over M1 either in isolation (intensity of 120 % rMT) or after a conditioning stimulus (80 % rMT) delivered, at different delays (ranging between 1–15 ms), over the ipsilateral PMv (Davare et al. 2008). We found that, at rest, PMv exerted a net inhibitory influence on M1 whereas, during power grip, this inhibition disappeared and was converted into a net facilitation during precision grip (Fig. 6.5). The fact that PMv–M1 interactions are selectively modulated during specific types of grasp provided further evidence that these connections play an important role in control of the hand (Davare et al. 2008). In the second study, we further investigated the functional connectivity between PMv and M1 during grasp of a series of real objects randomly presented



by a carousel and requiring either a precision grip or a whole-hand grasp (Davare et al. 2009). This study showed that, while subjects prepared to grasp, delivering a conditioning PMv pulse 6 or 8 ms before a test pulse over M1 strikingly facilitated motor-evoked potentials (MEPs) in the specific muscles that were used in the upcoming grasp (Fig. 6.6). This degree of facilitation correlated with the amount of muscle activity used later in the trial to grasp the objects. These results suggest that during grasp preparation PMv–M1 interactions are muscle-specific. PMv

appears to process the object geometrical properties relevant for the upcoming grasp, and transmits this information to M1, which in turn generates a motor command appropriate for the grasp.

While these two studies investigated the functional connectivity between PMv and M1, it still remains to elucidate the causal contribution of AIP to the PMv–M1 connectivity. In the third set of experiments (Davare et al. 2010), we developed a new technique of double-coil TMS combined with repetitive TMS to explore how information about an object to be grasped is transferred within the human AIP–PMv–M1 circuit. We investigated the consequences of AIP virtual lesions on PMv–M1 interactions at rest or during preparation to grasp objects with either a precision grip or a whole-hand grasp. PMv–M1 connectivity was probed by a double-coil TMS paradigm before and after continuous theta-burst TMS (cTBS) (Huang et al. 2005) was applied over AIP. At rest, AIP virtual lesions did not modify PMv–M1 interactions. In contrast, the usual muscle-specific PMv–M1 interactions that appeared during grasp preparation were significantly reduced following AIP cTBS without directly modifying corticospinal excitability (Fig. 6.6). Behaviourally, disruption of AIP was also associated with a relative loss of the grasp-specific pattern of digit muscle activity. These findings suggest that grasp-related and muscle-specific PMv–M1 interactions are driven by information about object properties provided by AIP. These results are important because they established that there is a causal transfer of information about object properties between AIP and PMv. In addition, this is a specific example of the more general effects of disrupting function in one part of a complex system on activation in remote areas. It extends previous work in the field (Bestmann et al. 2003, 2008a, 2008b) by employing direct electrophysiological measures of functional connectivity between remote areas to test how these change after a virtual lesion of a third area. This is important because it shows that movement deficits following disruption of a cortical area ‘A’ could result not from area A itself, but instead from an effect of that area on distant areas B or C or even on their respective interactions. Because a large frontoparietal network of areas is involved in the performance of hand movements (Castiello 2005; Grafton 2010; Davare et al. 2011), it could be that transient interference of one of these areas would yield interregional changes in connectivity within the cortical circuit.

Due to the reciprocal nature of AIP–PMv connections (Rizzolatti and Luppino 2001; Borra et al. 2008), it is possible that ‘canonical’ neurons in PMv acquire their grasp-selective properties through rapid recurrent feedback loops between PMv and AIP (Fig. 6.7). Moreover, if the motor command has to be updated, these recurrent loops would allow AIP to inform the motor output online, depending on the object’s new properties. Indeed, Buch et al. (2010) found that the right PMv–left M1 interactions could mediate information about how to adjust the grasp as soon as 75 ms after the object changed (Buch et al. 2010).

Another double-coil TMS study, carried out in resting volunteers, found that the intensity of the PMv conditioning stimulus modified its effect on the corticospinal excitability tested from M1 (Baumer et al. 2006). The recruitment of different PMv–M1 pathways by different TMS intensities might be influenced by the grasp

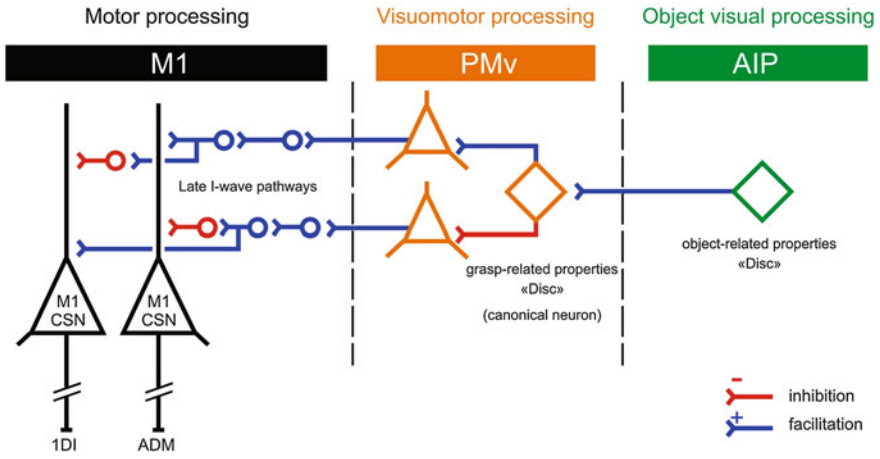


Fig. 6.7 Schematic model of connectivity between AIP, PMv and M1. PMv is connected with M1 corticospinal neurons (CSN; *black pyramids*) via indirect inhibitory (*red*) and facilitatory (*blue*) pathways (late I-wave pathways). The PMv output neurons (*orange pyramids*) giving rise to these pathways receive inhibitory and facilitatory connections from canonical neurons in PMv (*orange diamond*). Object-related neurons in AIP (*green diamond*) make facilitatory projections to canonical neurons in PMv. At rest, conditioning TMS over PMv reveals net inhibitory PMv–M1 interactions. When grasping the disc, the corresponding object-related neurons in AIP increase their firing rate, which facilitates in turn the appropriate canonical neurons in PMv. In this example, activation of the PMv canonical cell yields facilitation of the ADM muscle representation by down-regulating PMv–M1 inhibitory connections and up-regulating facilitatory PMv–M1 connections

context, bringing into play different neural populations involved in the task. Because the grasp-related information is represented in the PMv canonical neurons, a model of connectivity between PMv and M1 has been proposed in which the canonical neurons define a particular motor prototype by controlling the balance of inhibition/facilitation to complex muscle representations in M1 (Fig. 6.7). These representations are now known to be complex and overlapping in nature, with multiple representation of a given muscle that probably underpins the huge repertoire of human grasping actions (Schieber 2002; Rathelot and Strick 2006, 2009). Interestingly, mechanisms of surround inhibition might be responsible for selecting one type of action within the motor repertoire in M1 and it is possible that PMv inhibitory inputs to M1 contribute to these mechanisms. Recently, it has been shown that in patients with focal hand dystonia, PMv–M1 interactions are abolished (Houdayer et al. 2012). Because one of the main features of dystonia pathophysiology is the loss of cortical inhibition, it is reasonable to assume that abnormal PMv inputs to M1 are at least partly involved in the pathophysiology of dystonia.

Using the double-coil TMS paradigm, it is also possible to investigate the time course of a particular corticocortical interaction during movement planning. Koch et al. (2010) tested interactions between anterior and caudal regions of the IPS with

M1 when grasping objects in central or peripheral space. They found that the caudal part of IPS interacted with M1 early during the preparation of movements requiring a whole-hand grasp in the peripheral space. In contrast, the anterior portion of IPS interacted with M1 at a later stage and only for a precision grip, irrespective of object location (Koch et al. 2010). The pathways mediating these interactions are not obvious, since there are no known direct projections from the caudal IPS to M1.

Although most studies in this section examined brain connectivity during grasp of objects of different shapes, a recent study investigated the consequences of repetitive TMS applied over the left PMd on (1) the anticipatory coding of grip force when lifting objects of different weights and (2) its connectivity with M1, probed by measuring corticospinal excitability (van Nuenen et al. 2012). Subjects were asked to lift an object after a go-cue. An additional pre-cue correctly predicted the weight in 75 % of the cases. As expected, when the cues were incongruent, the grip force showed a systematic undershoot when the pre-cue prompted the preparation of a light lift. Conversely, there was a grip force overshoot if the pre-cue indicated a heavy lift. Using fMRI, the authors found that preparatory activity in the left PMd could predict the grip force undershoot but not overshoot. cTBS applied over the left PMd abolished the grip force undershoot, decreased corticospinal excitability and disrupted the relationship between PMd preparatory activity and the grip force. This suggests that PMd has a causal role in downscaling the grip force and reveals an inhibitory role of PMd in anticipatory grip force control during object lifting. New dual-site TMS paradigms have been used to probe the connectivity between PMd and the ipsilateral M1 using special coils (Groppa et al. 2012). At rest, PMd–M1 interactions revealed short-latency facilitation (1.2 ms), which was still present during a two-choice reaction time task but only when probing PMd–M1 interactions 125 ms after cue presentation. So far, it is difficult to interpret this short-latency PMd–M1 facilitation together with inhibitory effect of PMd on the grip force. Further experiments will be required to investigate PMd interactions with the cortical grasping circuit mediating predictive control of grip force.

6.6 Conclusions

This chapter has highlighted the growing knowledge and complexity of the cortical grasping network, and this undoubtedly reflects the biomechanical complexity of the reach-to-grasp action. Our understanding of the cortical grasping network continues to depend upon knowledge combined from the different experimental approaches possible in humans and non-human primates. The interrogation of the status of the connections within the grasping network is throwing new light on its operations, and is especially suited for determining the temporal evolution of activity within the network. Indeed, we should conclude by emphasising that this network operates on a very fast timescale. The evidence is that visual information

about an object can be incorporated into the selected grasping action in around 100–150 ms (Prabhu et al. 2007; Loh et al. 2010): objects therefore 'prime' likely motor responses without a great deal of preprocessing. This fast timescale is a challenge for fMRI studies, because although grasp- or reach-specific changes in BOLD will be detected, it is important to know that these changes actually reflect fast processing within the visuomotor circuits. Finally, there is also evidence that a different network, involving areas of the ventral stream, operates when memory-based information is used to guide the grasp (Kroliczak et al. 2007; Cohen et al. 2009).

References

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annu Rev Neurosci 25:189–220

Anderson KD (2004) Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma 21:1371–1383

Baumann MA, Fluet MC, Scherberger H (2009) Context-specific grasp movement representation in the macaque anterior intraparietal area. J Neurosci 29:6436–6448

Baumer T, Bock F, Koch G, Lange R, Rothwell JC, Siebner HR, Munchau A (2006) Magnetic stimulation of human premotor or motor cortex produces interhemispheric facilitation through distinct pathways. J Physiol 572:857–868

Baumer T, Schippling S, Kroeger J, Zittel S, Koch G, Thomalla G, Rothwell JC, Siebner HR, Orth M, Munchau A (2009) Inhibitory and facilitatory connectivity from ventral premotor to primary motor cortex in healthy humans at rest–a bifocal TMS study. Clin Neurophysiol 120:1724–1731

Begliomini C, Wall MB, Smith AT, Castiello U (2007) Differential cortical activity for precision and whole-hand visually guided grasping in humans. Eur J Neurosci 25:1245–1252

Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J (2003) Subthreshold high-frequency TMS of human primary motor cortex modulates interconnected frontal motor areas as detected by interleaved fMRI-TMS. Neuroimage 20:1685–1696

Bestmann S, Ruff CC, Blankenburg F, Weiskopf N, Driver J, Rothwell JC (2008a) Mapping causal interregional influences with concurrent TMS-fMRI. Exp Brain Res 191:383–402

Bestmann S, Swayne O, Blankenburg F, Ruff CC, Haggard P, Weiskopf N, Josephs O, Driver J, Rothwell JC, Ward NS (2008b) Dorsal premotor cortex exerts state-dependent causal influences on activity in contralateral primary motor and dorsal premotor cortex. Cereb Cortex 18:1281–1291

Binkofski F, Buccino G, Posse S, Seitz RJ, Rizzolatti G, Freund H (1999) A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. Eur J Neurosci 11:3276–3286

Borra E, Belmalih A, Calzavara R, Gerbella M, Murata A, Rozzi S, Luppino G (2008) Cortical connections of the macaque anterior intraparietal (AIP) area. Cereb Cortex 18:1094–1111

Boudrias MH, McPherson RL, Frost SB, Cheney PD (2010) Output properties and organization of the forelimb representation of motor areas on the lateral aspect of the hemisphere in rhesus macaques. Cereb Cortex 20:169–186

Brochier T, Spinks RL, Umilta MA, Lemon RN (2004) Patterns of muscle activity underlying object-specific grasp by the macaque monkey. J Neurophysiol 92:1770–1782

Buch ER, Mars RB, Boorman ED, Rushworth MF (2010) A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex during action reprogramming. J Neurosci 30:1395–1401

Bursztyn LL, Ganesh G, Imamizu H, Kawato M, Flanagan JR (2006) Neural correlates of internal-model loading. Curr Biol 16:2440–2445
Castiello U (2005) The neuroscience of grasping. Nat Rev Neurosci 6:726–736
Cavina-Pratesi C, Goodale MA, Culham JC (2007) FMRI reveals a dissociation between grasping and perceiving the size of real 3D objects. PLoS One 2:e424
Cavina-Pratesi C, Monaco S, Fattori P, Galletti C, McAdam TD, Quinlan DJ, Goodale MA, Culham JC (2010) Functional magnetic resonance imaging reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. J Neurosci 30:10306–10323
Cerri G, Shimazu H, Maier MA, Lemon RN (2003) Facilitation from ventral premotor cortex of primary motor cortex outputs to macaque hand muscles. J Neurophysiol 90:832–842
Chao LL, Martin A (2000) Representation of manipulable man-made objects in the dorsal stream. Neuroimage 12:478–484
Chouinard PA, Leonard G, Paus T (2005) Role of the primary motor and dorsal premotor cortices in the anticipation of forces during object lifting. J Neurosci 25:2277–2284
Cohen NR, Cross ES, Tunik E, Grafton ST, Culham JC (2009) Ventral and dorsal stream contributions to the online control of immediate and delayed grasping: a TMS approach. Neuropsychologia 47:1553–1562
Culham JC, Valyear KF (2006) Human parietal cortex in action. Curr Opin Neurobiol 16:205–212
Culham JC, Danckert SL, DeSouza JF, Gati JS, Menon RS, Goodale MA (2003) Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. Exp Brain Res 153:180–189
Dafotakis M, Sparing R, Eickhoff SB, Fink GR, Nowak DA (2008) On the role of the ventral premotor cortex and anterior intraparietal area for predictive and reactive scaling of grip force. Brain Res 1228:73–80
Daprati E, Sirigu A (2006) How we interact with objects: learning from brain lesions. Trends Cogn Sci 10:265–270
Davare M, Lemon R, Olivier E (2008) Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans. J Physiol 586:2735–2742
Davare M, Rothwell JC, Lemon RN (2010) Causal connectivity between the human anterior intraparietal area and premotor cortex during grasp. Curr Biol 20:176–181
Davare M, Kraskov A, Rothwell JC, Lemon RN (2011) Interactions between areas of the cortical grasping network. Curr Opin Neurobiol 21(4):565–570
Davare M, Andres M, Cosnard G, Thonnard JL, Olivier E (2006) Dissociating the role of ventral and dorsal premotor cortex in precision grasping. J Neurosci 26:2260–2268
Davare M, Andres M, Clerget E, Thonnard JL, Olivier E (2007) Temporal dissociation between hand shaping and grip force scaling in the anterior intraparietal area. J Neurosci 27:3974–3980
Davare M, Montague K, Olivier E, Rothwell JC, Lemon RN (2009) Ventral premotor to primary motor cortical interactions during object-driven grasp in humans. Cortex 45:1050–1057
De Renzi E, Motti F, Nichelli P (1980) Imitating gestures. A quantitative approach to ideomotor apraxia. Arch Neurol 37:6–10
Dominici F, Popa T, Ginanneschi F, Mazzocchio R, Rossi A (2005) Cortico-motoneuronal output to intrinsic hand muscles is differentially influenced by static changes in shoulder positions. Exp Brain Res 164:500–504
Dum RP, Strick PL (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. J Neurosci 11:667–689
Dum RP, Strick PL (2005) Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. J Neurosci 25:1375–1386
Ehrsson HH, Fagergren E, Forssberg H (2001) Differential fronto-parietal activation depending on force used in a precision grip task: an fMRI study. J Neurophysiol 85:2613–2623

Ehrsson HH, Fagergren A, Johansson RS, Forssberg H (2003) Evidence for the involvement of the posterior parietal cortex in coordination of fingertip forces for grasp stability in manipulation. J Neurophysiol 90:2978–2986

Ehrsson HH, Fagergren A, Jonsson T, Westling G, Johansson RS, Forssberg H (2000) Cortical activity in precision- versus power-grip tasks: an fMRI study. J Neurophysiol 83:528–536

Fattori P, Breveglieri R, Marzocchi N, Filippini D, Bosco A, Galletti C (2009) Hand orientation during reach-to-grasp movements modulates neuronal activity in the medial posterior parietal area V6A. J Neurosci 29:1928–1936

Fattori P, Raos V, Breveglieri R, Bosco A, Marzocchi N, Galletti C (2010) The dorsomedial pathway is not just for reaching: grasping neurons in the medial parieto-occipital cortex of the macaque monkey. J Neurosci 30:342–349

Flanagan JR, Wing AM (1997) The role of internal models in motion planning and control: evidence from grip force adjustments during movements of hand-held loads. J Neurosci 17:1519–1528

Fluet MC, Baumann MA, Scherberger H (2010) Context-specific grasp movement representation in macaque ventral premotor cortex. J Neurosci 30:15175–15184

Fogassi L, Gallese V, Buccino G, Craighero L, Fadiga L, Rizzolatti G (2001) Cortical mechanism for the visual guidance of hand grasping movements in the monkey: a reversible inactivation study. Brain 124:571–586

Frey SH, Vinton D, Norlund R, Grafton ST (2005) Cortical topography of human anterior intraparietal cortex active during visually guided grasping. Brain Res Cogn Brain Res 23:397–405

Gallese V, Murata A, Kaseda M, Niki N, Sakata H (1994) Deficit of hand preshaping after muscimol injection in monkey parietal cortex. NeuroReport 5:1525–1529

Glover S, Miall RC, Rushworth MF (2005) Parietal rTMS disrupts the initiation but not the execution of on-line adjustments to a perturbation of object size. J Cogn Neurosci 17:124–136

Goodale MA, Meenan JP, Bulthoff HH, Nicolle DA, Murphy KJ, Racicot CI (1994) Separate neural pathways for the visual analysis of object shape in perception and prehension. Curr Biol 4:604–610

Grafton ST (2010) The cognitive neuroscience of prehension: recent developments. Exp Brain Res 204:475–491

Grol MJ, Majdandzic J, Stephan KE, Verhagen L, Dijkerman HC, Bekkering H, Verstraten FA, Toni I (2007) Parieto-frontal connectivity during visually guided grasping. J Neurosci 27:11877–11887

Groppa S, Werner-Petroll N, Munchau A, Deuschl G, Ruschworth MF, Siebner HR (2012) A novel dual-site transcranial magnetic stimulation paradigm to probe fast facilitatory inputs from ipsilateral dorsal premotor cortex to primary motor cortex. Neuroimage 62:500–509

Haaland KY, Elsinger CL, Mayer AR, Durgerian S, Rao SM (2004) Motor sequence complexity and performing hand produce differential patterns of hemispheric lateralization. J Cogn Neurosci 16:621–636

He SQ, Dum RP, Strick PL (1993) Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. J Neurosci 13:952–980

Houdayer E, Beck S, Karabanov A, Poston B, Hallett M (2012) The differential modulation of the ventral premotor-motor interaction during movement initiation is deficient in patients with focal hand dystonia. Eur J Neurosci 35:478–485

Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005) Theta burst stimulation of the human motor cortex. Neuron 45:201–206

Jeannerod M, Arbib MA, Rizzolatti G, Sakata H (1995) Grasping objects: the cortical mechanisms of visuomotor transformation. Trends Neurosci 18:314–320

Jenmalm P, Schmitz C, Forssberg H, Ehrsson HH (2006) Lighter or heavier than predicted: neural correlates of corrective mechanisms during erroneously programmed lifts. J Neurosci 26:9015–9021

Johansson RS, Westling G (1984) Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. Exp Brain Res 56:550–564

Johansson RS, Westling G (1988) Coordinated isometric muscle commands adequately and erroneously programmed for the weight during lifting task with precision grip. Exp Brain Res 71:59–71

Johansson RS, Flanagan JR (2009) Coding and use of tactile signals from the fingertips in object manipulation tasks. Nat Rev Neurosci 10:345–359

Johnson-Frey SH, Newman-Norlund R, Grafton ST (2005) A distributed left hemisphere network active during planning of everyday tool use skills. Cereb Cortex 15:681–695

Johnston JA, Bobich LR, Santello M (2010) Coordination of intrinsic and extrinsic hand muscle activity as a function of wrist joint angle during two-digit grasping. Neurosci Lett 474:104–108

Koch G, Franca M, Del Olmo MF, Cheeran B, Milton R, Alvarez Sauco M, Rothwell JC (2006) Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. J Neurosci 26:7452–7459

Koch G, Fernandez Del Olmo M, Cheeran B, Ruge D, Schippling S, Caltagirone C, Rothwell JC (2007) Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. J Neurosci 27:6815–6822

Koch G, Fernandez Del Olmo M, Cheeran B, Schippling S, Caltagirone C, Driver J, Rothwell JC (2008) Functional interplay between posterior parietal and ipsilateral motor cortex revealed by twin-coil transcranial magnetic stimulation during reach planning toward contralateral space. J Neurosci 28:5944–5953

Koch G, Cercignani M, Pecchioli C, Versace V, Oliveri M, Caltagirone C, Rothwell J, Bozzali M (2010) In vivo definition of parieto-motor connections involved in planning of grasping movements. Neuroimage 51:300–312

Koski L, Iacoboni M, Mazziotta JC (2002) Deconstructing apraxia: understanding disorders of intentional movement after stroke. Curr Opin Neurol 15:71–77

Kroliczak G, Cavina-Pratesi C, Goodman DA, Culham JC (2007) What does the brain do when you fake it? An FMRI study of pantomimed and real grasping. J Neurophysiol 97:2410–2422

Lemon RN (2008) Descending pathways in motor control. Annu Rev Neurosci 31:195–218

Lemon RN, Johansson RS, Westling G (1995) Corticospinal control during reach, grasp, and precision lift in man. J Neurosci 15:6145–6156

Loh MN, Kirsch L, Rothwell JC, Lemon RN, Davare M (2010) Information about the weight of grasped objects from vision and internal models interacts within the primary motor cortex. J Neurosci 30:6984–6990

Matsumura M, Sawaguchi T, Oishi T, Ueki K, Kubota K (1991) Behavioral deficits induced by local injection of bicuculline and muscimol into the primate motor and premotor cortex. J Neurophysiol 65:1542–1553

Murata A, Gallese V, Luppino G, Kaseda M, Sakata H (2000) Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. J Neurophysiol 83:2580–2601

Murata A, Fadiga L, Fogassi L, Gallese V, Raos V, Rizzolatti G (1997) Object representation in the ventral premotor cortex (area F5) of the monkey. J Neurophysiol 78:2226–2230

Nowak DA, Hermsdorfer J, Topka H (2003) Deficits of predictive grip force control during object manipulation in acute stroke. J Neurol 250:850–860

Nowak DA, Hermsdorfer J, Marquardt C, Fuchs HH (2002) Grip and load force coupling during discrete vertical arm movements with a grasped object in cerebellar atrophy. Exp Brain Res 145:28–39

Prabhu G, Voss M, Brochier T, Cattaneo L, Haggard P, Lemon R (2007) Excitability of human motor cortex inputs prior to grasp. J Physiol 581:189 –201

Raos V, Umilta MA, Gallese V, Fogassi L (2004) Functional properties of grasping-related neurons in the dorsal premotor area F2 of the macaque monkey. J Neurophysiol 92:1990–2002

Raos V, Umilta MA, Murata A, Fogassi L, Gallese V (2006) Functional properties of grasping-related neurons in the ventral premotor area F5 of the macaque monkey. J Neurophysiol 95:709–729

Rathelot JA, Strick PL (2006) Muscle representation in the macaque motor cortex: an anatomical perspective. Proc Natl Acad Sci U S A 103:8257–8262

Rathelot JA, Strick PL (2009) Subdivisions of primary motor cortex based on cortico-motoneuronal cells. Proc Natl Acad Sci U S A 106:918–923

Rice NJ, Tunik E, Grafton ST (2006) The anterior intraparietal sulcus mediates grasp execution, independent of requirement to update: new insights from transcranial magnetic stimulation. J Neurosci 26:8176–8182

Rizzolatti G, Luppino G (2001) The cortical motor system. Neuron 31:889–901

Sack AT (2006) Transcranial magnetic stimulation, causal structure-function mapping and networks of functional relevance. Curr Opin Neurobiol 16:593–599

Sakata H, Taira M, Murata A, Mine S (1995) Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. Cereb Cortex 5:429–438

Schieber MH (2002) Motor cortex and the distributed anatomy of finger movements. Adv Exp Med Biol 508:411–416

Schluter ND, Rushworth MF, Passingham RE, Mills KR (1998) Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. Brain 121(Pt 5):785–799

Schmidlin E, Brochier T, Maier MA, Kirkwood PA, Lemon RN (2008) Pronounced reduction of digit motor responses evoked from macaque ventral premotor cortex after reversible inactivation of the primary motor cortex hand area. J Neurosci 28:5772–5783

Shimazu H, Maier MA, Cerri G, Kirkwood PA, Lemon RN (2004) Macaque ventral premotor cortex exerts powerful facilitation of motor cortex outputs to upper limb motoneurons. J Neurosci 24:1200–1211

Stark E, Asher I, Abeles M (2007) Encoding of reach and grasp by single neurons in premotor cortex is independent of recording site. J Neurophysiol 97:3351–3364

Tallis R (2003) The hand: a philosophical inquiry in human being. Edinburgh University Press, Edinburgh

Tomassini V, Jbabdi S, Klein JC, Behrens TE, Pozzilli C, Matthews PM, Rushworth MF, Johansen-Berg H (2007) Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. J Neurosci 27:10259–10269

Tunik E, Frey SH, Grafton ST (2005) Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. Nat Neurosci 8:505–511

Umilta MA, Brochier TG, Spinks RL, Lemon RN (2007) Simultaneous recording of macaque premotor and primary motor cortex neuronal populations reveals different functional contributions to visuomotor grasp. J Neurophysiol 98:488–501

van Nuenen BF, Kuhtz-Buschbeck J, Schulz C, Bloem BR, Siebner HR (2012) Weight-specific anticipatory coding of grip force in human dorsal premotor cortex. J Neurosci 32:5272–5283

Verhagen L, Dijkerman HC, Grol MJ, Toni I (2008) Perceptuo-motor interactions during prehension movements. J Neurosci 28:4726–4735

Witney AG, Goodbody SJ, Wolpert DM (2000) Learning and decay of prediction in object manipulation. J Neurophysiol 84:334–343

Wolpert DM, Flanagan JR (2001) Motor prediction. Curr Biol 11:R729–R732

Chapter 7
Modulation of Functional Connectivity with Transcranial Direct Current Stimulation

Rafael Polanía, Michael A. Nitsche and Walter Paulus

Abstract Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation tool suited to alter cortical excitability and activity via application of direct currents. The long-lasting synaptic modifications induced by this stimulation technique have been shown to result in behavioral functional improvements. This might be related to tDCS-induced modulations of associations among populations of neurons which improve the functional connectivity between local and segregated cortical areas involved in the respective functional networks. In this chapter, we describe the effects of tDCS-induced neuroplasticity on human brain functional networks at the large-scale level, and how different functional connectivity techniques might be used to track for such induced alterations.

7.1 Introduction

The brain's ability to constantly reorganize itself by forming new neural connections during development and in response to environmental stimuli or brain injuries is called neuroplasticity. From a general point of view, this process works in a pruning-like way, where inefficient or infrequently activated synaptic connections are weakened or eliminated, while highly routed information paths are preserved or strengthened (Citri and Malenka 2008; Malenka and Bear 2004). In the last decade, tDCS has been reintroduced as a noninvasive brain stimulation tool suited to alter cortical excitability and activity via the application of weak

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direct currents (Nitsche et al. 2007, 2003a; Nitsche and Paulus 2000, 2001). This technique offers the possibility of noninvasively inducing reversible long-term plastic alterations in vivo, thus allowing us to study these phenomena in humans. In addition to the physiological effects, tDCS has been shown to modulate plasticity-related functions, such as motor learning, visuo-motor coordination, memory, nondominant hand function (Antal et al. 2004a, b; Boggio et al. 2006; Marshall et al. 2006; Nitsche et al. 2003b), and improve motor function in stroke patients, among others (Fregni et al. 2005; Hummel et al. 2005; Jo et al. 2009). However, the effects underlying tDCS-induced modulations in the human brain, which are afterward reflected in modulations of behavior, remain incompletely understood.

The human brain has been shown to exhibit functional interconnection patterns linking whole brain regions, cell populations, and individual cortical neurons (Salin and Bullier 1995). Further analysis provides evidence that such interconnection patterns are neither completely regular nor completely random, thus reflecting an integration of both localized and segregated information processing (Sporns and Zwi 2004; Strogatz 2001). Additionally, such organization at both microscopic and large-scale level was demonstrated to present a highly efficient information transfer with nearly minimal wiring costs (Achard and Bullmore 2007). Electrophysiological and neuroimaging methods such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) have been used as tools to noninvasively acquire information regarding the neural activity of the brain with their respective spatial–temporal advantages and disadvantages. In the last decade, these methods have been used as powerful tools to study the architecture of human brain functional networks at the large scale level.

One important aspect of the tDCS-induced functional effects might be a modulation of learning-related synaptic connections. Hereby, tDCS-induced effects might modulate functional connectivity between segregated cortical areas in the task under study. Hence, the use of methods such as EEG and fMRI combined with noninvasive brain stimulation might be an appropriate starting point to elucidate the impact of tDCS-induced neuroplasticity on human brain functional networks. The following section provides insights on how different functional connectivity methods can be used to track for tDCS-induced neuroplastic alterations in the human brain.

7.2 Functional Connectivity

The human brain can be conceptualized as a set of elements (e.g. neuronal populations) that spatially and temporally interact with each other, i.e. a functional network. These functional networks present several major organizational principles which can be summarized by the following two points: First, a vast number of GABAergic connections at the local/neighbor level intrinsically organize center-surround functional units that can influence discrete action primitives at a lower

level (Kujirai et al. 1993). And second, glutamatergic projections to more distal targets (e.g. via trans-callosal or intracortical fibers) conglomerate these GABAergically controlled functional units into larger cooperative groups and organize action primitives into more complex networks (Fox and Raichle 2007; Fox et al. 2005, 2007). Hence, brain networks can be abstracted at three different levels:

1. The *micro-scale* level, which is the level of individual cells and synapses
2. The level of neuronal populations or *meso-scale* level
3. The level of interanatomically connected regions or *large-scale* level

Noninvasive electrophysiological and neuroimaging methods such as EEG and fMRI allow to study human functional networks at the meso- and large-scale level. EEG has a relatively poor spatial resolution (few tenths up to $\sim$300 of recording channels can be placed over the whole scalp), however it allows to record neural activity at a high temporal resolution (milliseconds), thus allowing the study of brain rhythms at specific frequency bands. On the other hand, fMRI has a low temporal resolution (in the order of seconds); however, it allows to study the hemodynamic activity of neural populations, which is often correlated with neuronal activity (Crone et al. 2006; Logothetis 2002) at a finer resolution (millimeters). Thus, both methods are used to study the influence of tDCS on different aspects of functional networks in a noninvasive way. In the following subsections, we introduce several methods that have been used to study tDCS-induced modulations of brain functional connectivity using neuroimaging.

7.2.1 Seed Connectivity Analysis

Functional connectivity of the spontaneous cerebral activity measured by BOLD-fMRI has enhanced our understanding of the human brain functional architecture. Analysis with resting state fMRI (rs-fMRI) shows consistent large-scale patterns of coherent signals which correlate with the underlying structural and functional anatomy of brain regions related to task performance (see an example in Fig. 7.1).

Hence, a priori selection of a region of interest (ROI) may allow the study of the functional architecture and its modulation, e.g. by brain stimulation techniques, of a given cerebral area. In a recent study by Polania et al. (2011), an a priori selection of ROIs belonging to different striatal and thalamic regions was performed, and afterward independent seed functional connectivity analyses for each of the ROIs were carried out in order to track for possible cortico-subcortical functional modulations. The results of this study show that excitatory anodal stimulation over M1 induces a modulation of the cortico-striato-thalamo-cortical functional motor circuit by increasing the functional coupling between the ipsilateral stimulated M1 and thalamus (Fig. 7.2a), accompanied by a reduction of functional coupling between the striatum and key elements of the default mode network (which is a network that that reduces its activity during task performance) (Fig. 7.2b). The connectivity reduction of elements belonging to the default mode network might be caused by the

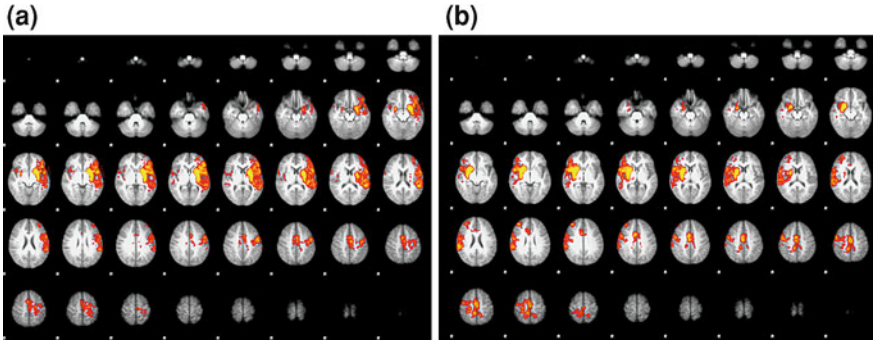

Fig. 7.1 Shown is the functional connectivity analysis of rs-FMRI data using the *left* (**a**) and *right* (**b**) putamen as seed ROI. Activations (*hot colors*) represent regions where activity highly correlates with the putamen. As expected, prefrontal, temporal, and motor-related cortical areas appear to be highly synchronized with the putamen. Notice the lateralization of the activations when left or right putamen is used as seed ROI

stimulation-induced motor-loop activation, which presumably mimics cerebral correlates of motor behavior to some extent. Interestingly, a recent study by Benninger et al. (2010) shows that anodal tDCS applied over M1 improves gait and bradykinesia in patients suffering from Parkinson's disease. The investigators hypothesized that thalamic activity could be theoretically modulated by cortical stimulation. Indeed, our results suggest that there seems to be a connectivity-driven alteration of thalamo-cortical activity caused by tDCS over the primary motor cortex, being in favor for connectivity-driven indirect effects of tDCS on thalamic functions. Thus, with the results of Polania and colleagues (2011) it can be suggested that excitatory anodal stimulation over M1 induces a general activation of motor task-related cortico-subcortical related functional networks.

7.2.2 Independent Component Analysis

The most common way to explore changes or modulations of the functional architecture of brain networks by aid of rs-FMRI in a model-free way (i.e. no a priori assumptions are required like in seed connectivity analysis) is independent component analysis (ICA). Using this technique, the maximally statistically independent, non-Gaussian components from fMRI data are detected by optimizing a measure of non-Gaussianity in the estimated brain maps. Using this technique, recent studies have demonstrated that resting state networks (components) are modulated after implicit motor learning and memory consolidation tasks (Albert et al. 2009a, b). However, no published tDCS studies have made use of this technique to investigate tDCS-induced modulations of functional networks. A disadvantage of this approach is, however, that the analysis is spatially restricted to the functional networks identified by ICA. This means that if a tDCS-induced

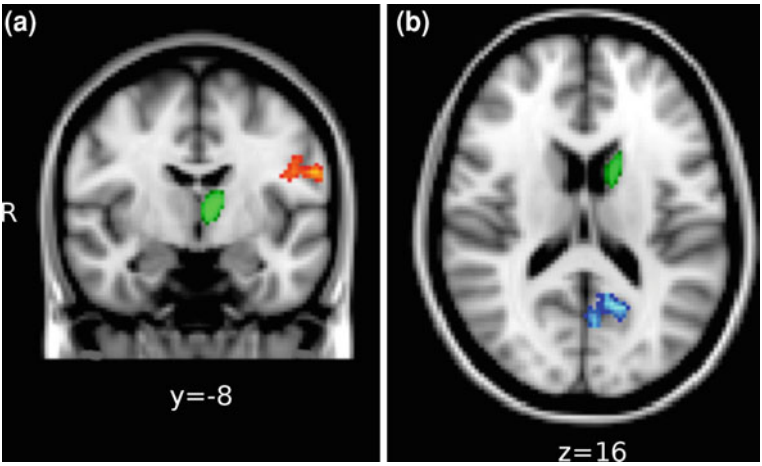

Fig. 7.2 After anodal stimulation was applied over the left primary motor cortex, the left thalamus (*green* region in panel **a**) significantly increased the functional coupling with its ipsilateral motor and premotor cortex (*hot colors* in panel **a**). Interestingly, the functional coupling between left caudate nucleus (*green* region panel **b**) and left posterior cingulated cortex significantly decreased (*cold colors* panel **b**)

modulation takes place in networks not previously identified by ICA, the respective tDCS-induced alterations might not be observed by the use of this technique. One way to cope with this problem is the use of graph theory.

7.2.3 Graph Theory

In the last decade, characterization of human brain functional networks has taken increasingly advantage from graph theory as mathematical approach (Bullmore and Sporns 2009; Bullmore and Bassett 2011). A graph is defined as the abstract representation of a network consisting of a set of elements (vertices or *nodes*) linked by a set of connections (*edges*). In EEG studies, each node is represented by a recording electrode and in fMRI studies nodes are represented by the mean BOLD activity of a region or a single voxel. The edges represent functionally connected brain regions which are identified by correlation methods (either linear or non-linear). The first step to build a brain functional network is to calculate the correlation measure between all pair-wise combinations of the functional time-series of the graph nodes, thus resulting in a $N \times N$ synchronization matrix. Then, for each M a connectivity graph G is formed consisting of N nodes and a set of undirected edges E (functional connectivity) by applying a correlation threshold T to M:

$$e_{ij} = \begin{cases} 1 & \text{if } M_{ij} > T \\ 0 & \text{otherwise} \end{cases}$$

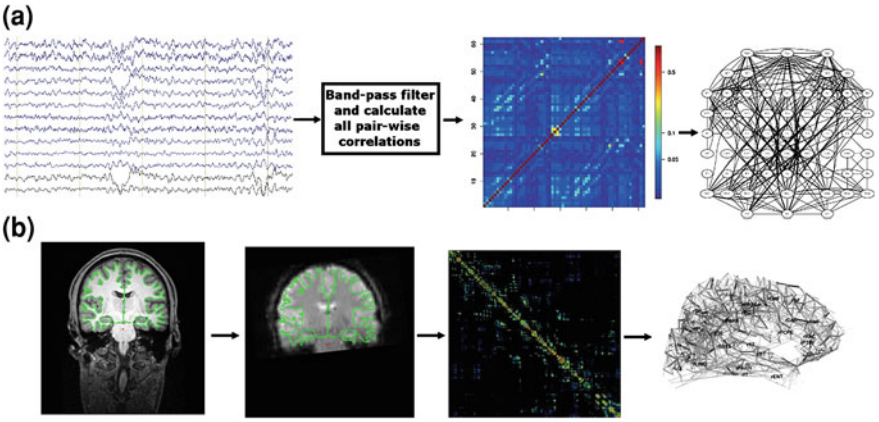

Fig. 7.3 Simplified illustration of the generation of graph based on the functional information of EEG and fMRI recordings. **a** EEG-epochs are first band-pass filtered in the frequency band of interest. Then the synchronization index of all pair-wise combinations of all EEG channels are calculated, and "stored" in a synchronization matrix. A threshold is set to this matrix and the pairs of channels showing suprathreshold correlations are said to be connected. **b** Graphs based on fMRI data are built in a similar way. The main difference is that the nodes are the gray matter voxels containing BOLD-fMRI time courses. The typical number of gray matter voxels in a human brain at a 3 mm^3 resolution is ~ 16000

Hence, if the correlation values between a pair of nodes (EEG channel or gray matter voxel for fMRI) i and j is greater than the given value T, an edge is said to exist. Simplified examples on how to build graphs from EEG and fMRI functional data are depicted in Fig. 7.3

Once the graph is built, different parameters can be defined to characterize the architecture of a graph. Here, we mention some few basic parameters that may be used to characterize graph architecture:

- *Connectivity degree.* Number of edges per node. The average of the connectivity degree of every node in the graph is defined as the mean connectivity degree.
- *Distance.* The distance *d(i, j)* between two nodes i and j is defined as the minimum number of edges required to go from one node to the other.
- *Characteristic path length.* The nodal characteristic path length L_i of a given node I can be defined in the following way:

$$L_i = \frac{\sum_{j=1;\, i \neq j}^{N} d(i,j)}{N-1}$$

The mean of all shortest distances connecting all pair of nodes in a graph is defined as the characteristic path length L. The smaller this value is, the more efficient is the network communication.

- *Clustering coefficient.* The nodal clustering coefficient C_i can be defined in the following way

$$C_i = \frac{\#\text{edges\_in\_}\hat{G}_i}{\frac{1}{2}k_i(k_i - 1)}$$

where G_i is the subgraph formed by the node i and its direct neighbors. The clustering coefficient C is defined as the mean of all C_i. This parameter provides information regarding the efficacy of the local connectedness of a network.

In this chapter, we restrict to these four basic parameters. Additional information regarding graph theory applied to neuroscience can be found elsewhere (Bullmore and Sporns 2009; Bullmore and Bassett 2011; Sporns et al. 2004; Sporns and Zwi 2004; Stam 2010; Stam and Reijneveld 2007). In the following section, it is shown how graph theory can be used to track for neuroplastic alterations induced by tDCS by means of EEG and fMRI.

7.3 Tracking for tDCS-Induced Modulations Using Graph Theory

In a recent study, Polania and colleagues (2011b) used EEG recordings during the performance of simple voluntary hand movements to evaluate the impact of excitatory anodal tDCS over the primary motor cortex (M1) on functional cortical networks. The authors found a remarkable increase in synchronization of regions involved in motor task performance only in the high-gamma frequency band (60–90 Hz). This finding is interesting considering that high-gamma oscillations have demonstrated to be induced during motor and sensorimotor processes in task-related brain regions (Omlor et al. 2007; Schoffelen et al. 2005). In further accordance, recordings with electrocorticograms have shown voluntary movement-related increases in motor and premotor areas (Brovelli et al. 2005) which were confirmed by noninvasive recordings (EEG and MEG) (Tecchio et al. 2008; Waldert et al. 2008). Thus, it can be speculated that a tDCS-induced increase of functional synchronization is an important aspect for the beneficial effects of anodal tDCS on implicit and explicit motor learning (Nitsche et al. 2003b; Reis et al. 2009), motor training effects and nondominant hand function in humans (Boggio et al. 2006), together with recovery of hand function in stroke patients (Boggio et al. 2007; Grefkes and Fink 2011; Hummel et al. 2005; Hummel and Cohen 2005). Altogether, we hypothesize that the excitability increase induced by anodal stimulation over the primary motor cortex (Nitsche and Paulus 2000, 2001) might be related to an enhancement in the strengthening of dynamical task-related synaptic connections. These strengthened connections over the anodal-stimulated region appear to be specifically related to a topological functional reorganization in the frequency band of the task under study. Further studies are required to confirm this hypothesis (Fig. 7.4).

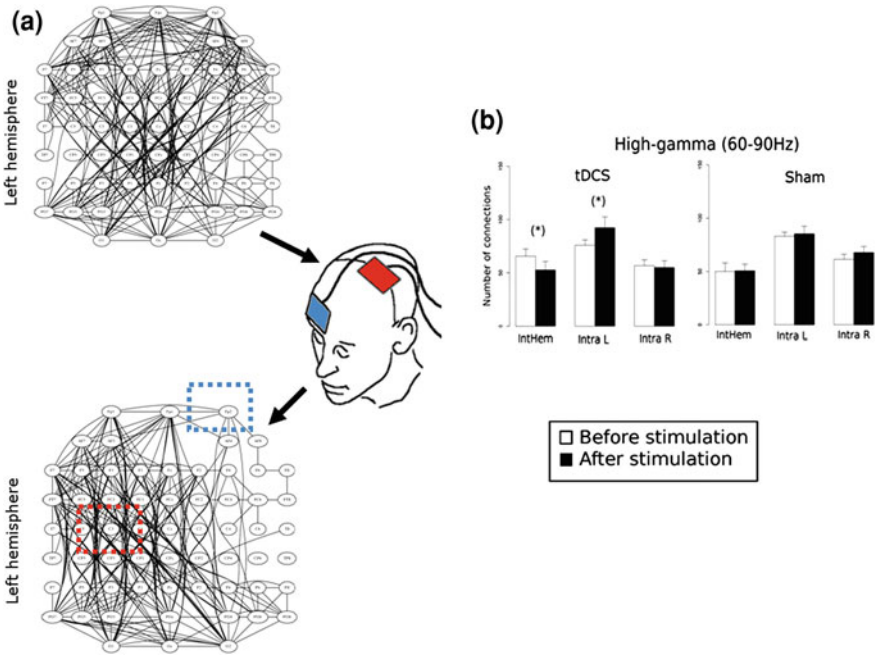

Fig. 7.4 64 channel EEG recordings were acquired during simple right-hand finger tapping before and after the application of 10 min anodal tDCS (*red*) over the left primary motor cortex. Synchronization matrices were calculated (using the synchronization likelihood as a synchronization index (Stam and Dijk 2002)) and transformed to undirected graphs thresholded at a mean connectivity degree $K = 10$ (Polania et al. 2011a). **a** After the end of stimulation, functional connectivity significantly increased in the left hemisphere in the high-gamma band (60–90 Hz). **b** Number of inter- and intra-hemispheric connections were quantified and compared before and after real and sham stimulation. The number of left intrahemispheric connections increases significantly in the left hemisphere, whereas the number of inter-hemispheric connections significantly decreases after the application of tDCS in the high-gamma band during right-hand finger tapping

In a subsequent study, Polania and colleagues attempted to track for tDCS-induced neuroplastic alterations by studying changes in the functional architecture of networks based on resting state BOLD-fMRI (Polania et al. 2011b). The authors acquired resting state fMRI data sets in healthy volunteers before and after the application of anodal tDCS over M1, placing the reference electrode over the contralateral orbit. Undirected graphs were built at the voxel resolution level (i.e. each gray matter voxel represented a node) and the nodal connectivity degree and minimum path length were compared in a normalized brain before and after the application of tDCS. The results revealed a decrease of the long distance topological functional connections between the left M/S1 and the rest of the brain, i.e. the minimum path length significantly increased in the left M/S1. This finding is interesting, considering that the primary mechanisms for anodal tDCS-induced excitability is subthreshold membrane depolarization, resulting in an increase of the spontaneous activity of the stimulated region (Bindman et al. 1964; Purpura and McMurtry 1965). Thus it was speculated that the local increase of

spontaneous activity decreases the signal to noise ratio, and consequently decreases synchronization of the stimulated area with long-distance functional connected brain regions. When a seed connectivity analysis was carried out using the left M/S1 as seed ROI, ipsilateral motor performance-related cortical areas (premotor, motor and superior parietal areas) showed enhanced connectivity with the seed region (as compared to the situation before tDCS), which might mimic task-related activation, thus resulting in a decoupling of sparse distant functional connected regions—a decrease in functional connectivity between left M/S1 region and contralateral cortical areas was observed following tDCS. It is important to notice that the graph theoretical analysis was solely based on resting state fMRI measurements.

The results of the studies presented in this section indicate that tDCS-induced neuroplastic alterations might be related to changes in functional connectivity. Moreover, we have shown that graph theory might be a powerful approach to track for stimulation-induced functional alterations in the human brain. Nevertheless, we believe that this technique should be accompanied with seed connectivity analysis, and ICA to gain more information about the functional state of the brain.

7.4 Conclusions and Future Work

Taken together, the results of the above-mentioned studies show that long-lasting synaptic modifications induced by tDCS, which result in behavioral improvements, might include an alteration of associations among populations of neurons involved in the respective task-relevant functional networks. So far, the influence of tDCS applied over M1 on functional connectivity was studied during rest and the performance of simple motor tasks. However, when tDCS is applied over M1 during task performance, it has been shown to improve implicit and explicit motor learning (Nitsche et al. 2003b; Reis et al. 2009) and when applied to other cortical areas e.g. dorso-lateral-prefrontal-cortex (DLPFC) it has been shown to modulate working-memory task performance (Fregni et al. 2005) and decision making (Fecteau et al. 2007; Hecht et al. 2010). Thus it is tempting to speculate that tDCS-induced changes of functional connectivity are causally related to alterations of cognitive functions generated by this stimulation. This should be explored to a larger degree in future studies. Combining cognitive task performance with tDCS and EEG/fMRI-based functional connectivity analysis might be a promising approach. Apart from the presumed interactions in healthy humans, this might also be important with regard to the clinical application of tDCS.

In clinical studies using graph theory, a functional connectivity loss has been described in patients suffering from stroke, Alzheimer's disease (AD), and multiple sclerosis (MS) (Helekar et al. 2010; Jelsone-Swain et al. 2010; Stam et al. 2007; Westlake and Nagarajan 2011). Interestingly, application of tDCS:

- over M1 enhances motor function in stroke patients (Hummel et al. 2005)
- over temporal cortex enhances working memory in AD (Boggio et al. 2009)
- over M1 modulates pain (Mori et al. 2010; Antal et al. 2010).

Thus in future studies it should be explored whether tDCS would modulate functional connectivity and induce synchronization changes in diseases that have been demonstrated to have disrupted functional and structural networks relative to healthy subjects using graph theory as a noninvasive tool to track for functional recovery and to correlate these changes with behavioral improvements. Also here, revealing the importance of tDCS-induced modulations of functional connectivity will be important to understand how tDCS improves cognitive and motor functions in these patients, and help to develop optimized stimulation protocols. Hence, the establishment of functional connectivity alteration measurements as a potentially important effect of brain stimulation techniques might help to understand the effects of stimulation on functions to a larger degree. Moreover, combination of brain stimulation with functional connectivity analysis might also help to identify relevant functional networks in health and disease, and their influence on behavioral outcomes.

References

Achard S, Bullmore E (2007) Efficiency and cost of economical brain functional networks. PLoS Comput Biol 3(2):e17

Albert NB, Robertson EM, Mehta P, Miall RC (2009a) Resting state networks and memory consolidation. Commun Integr Biol 2(6):530–532

Albert NB, Robertson EM, Miall RC (2009b) The resting human brain and motor learning. Curr Biol 19(12):1023–1027

Antal A, Terney D, Kuhnl S, Paulus W (2010) Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manag 39(5):890–903

Antal A, Nitsche MA, Kincses TZ, Kruse W, Hoffmann KP, Paulus W (2004a) Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extra striate visual areas in humans. Eur J Neurosci 19(10):2888–2892

Antal A, Nitsche MA, Kruse W, Kincses TZ, Hoffmann KP, Paulus W (2004b) Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. J Cogn Neurosci 16(4):521–527

Bindman LJ, Lippold OC, Redfearn JW (1964) The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. J Physiol 172:369–382

Boggio PS, Castro LO, Savagim EA, Braite R, Cruz VC, Rocha RR, Rigonatti SP, Silva MT, Fregni F (2006) Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. Neurosci Lett 404(1–2):232–236

Boggio PS, Khoury LP, Martins DC, Martins OE, de Macedo EC, Fregni F (2009) Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. J Neurol Neurosurg Psychiatry 80(4):444–447

Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F (2007) Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. Restor Neurol Neurosci 25(2):123–129

Brovelli A, Lachaux JP, Kahane P, Boussaoud D (2005) High gamma frequency oscillatory activity dissociates attention from intention in the human premotor cortex. Neuroimage 28(1):154–164

Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10(3):186–198

Bullmore ET, Bassett DS (2011) Brain graphs: graphical models of the human brain connectome. Ann Rev Clin Psychol 7:113–140

Citri A, Malenka RC (2008) Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology 33(1):18–41

Crone NE, Sinai A, Korzeniewska A (2006) High-frequency gamma oscillations and human brain mapping with electrocorticography. Prog Brain Res 159:275–295

Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A (2007) Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci 27(46):12500–12505

Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8(9):700–711

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 102(27):9673–9678

Fox MD, Snyder AZ, Vincent JL, Raichle ME (2007) Intrinsic fluctuations within cortical systems account for intertrial variability in human behavior. Neuron 56(1):171–184

Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MT, Paulus W (2005) Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 166(1):23–30

Grefkes C, Fink GR (2011) Reorganization of cerebral networks after stroke: new insights from neuroimaging with connectivity approaches. Brain 134(Pt 5):1264–1276

Hecht D, Walsh V, Lavidor M (2010) Transcranial direct current stimulation facilitates decision making in a probabilistic guessing task. J Neurosci 30(12):4241–4245

Helekar SA, Shin JC, Mattson BJ, Bartley K, Stosic M, Saldana-King T, Montague PR, Hutton GJ (2010) Functional brain network changes associated with maintenance of cognitive function in multiple sclerosis. Front Hum Neurosci 4:219

Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, Cohen LG (2005) Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 128(Pt 3):490–499

Hummel F, Cohen LG (2005) Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. Neurorehabil Neural Repair 19(1):14–19

Jelsone-Swain LM, Fling BW, Seidler RD, Hovatter R, Gruis K, Welsh RC (2010) Reduced interhemispheric functional connectivity in the motor cortex during rest in limb-onset amyotrophic lateral sclerosis. Front Syst Neurosci 4:158

Jo JM, Kim YH, Ko MH, Ohn SH, Joen B, Lee KH (2009) Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehabil 88(5):404–409

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501–519

Logothetis NK (2002) The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. Philos Trans R Soc Lond B Biol Sci 357(1424):1003–1037

Malenka RC, Bear MF (2004) LTP and LTD: an embarrassment of riches. Neuron 44(1):5–21

Marshall L, Helgadottir H, Molle M, Born J (2006) Boosting slow oscillations during sleep potentiates memory. Nature 444(7119):610–613

Mori F, Codeca C, Kusayanagi H, Monteleone F, Buttari F, Fiore S, Bernardi G, Koch G, Centonze D (2010) Effects of anodal transcranial direct current stimulation on chronic neuropathic pain in patients with multiple sclerosis. J Pain 11(5):436–442

Nitsche MA, Doemkes S, Karakose T, Antal A, Liebetanz D, Lang N, Tergau F, Paulus W (2007) Shaping the effects of transcranial direct current stimulation of the human motor cortex. J Neurophysiol 97(4):3109–3117

Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W (2003a) Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects. Suppl Clin Neurophysiol 56:255–276

Nitsche MA, Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 527(Pt 3):633–639

Nitsche MA, Paulus W (2001) Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57(10):1899–1901

Nitsche MA, Schauenburg A, Lang N, Liebetanz D, Exner C, Paulus W, Tergau F (2003b) Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J Cogn Neurosci 15(4):619–626

Omlor W, Patino L, Hepp-Reymond MC, Kristeva R (2007) Gamma-range corticomuscular coherence during dynamic force output. Neuroimage 34(3):1191–1198

Polanía R, Paulus W, Nitsche MA (2011) Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp doi: 10.1002/hbm.21380

Polania R, Nitsche MA, Paulus W (2011a) Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. Hum Brain Mapp 32(8):1236–1249

Polania R, Paulus W, Antal A, Nitsche MA (2011b) Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. Neuroimage 54(3):2287–2296

Purpura DP, McMurtry JG (1965) Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol 28:166–185

Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, Celnik PA, Krakauer JW (2009) Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A 106(5):1590–1595

Salin PA, Bullier J (1995) Corticocortical connections in the visual system: structure and function. Physiol Rev 75(1):107–154

Schoffelen JM, Oostenveld R, Fries P (2005) Neuronal coherence as a mechanism of effective corticospinal interaction. Science 308(5718):111–113

Sporns O, Chialvo DR, Kaiser M, Hilgetag CC (2004) Organization, development and function of complex brain networks. Trends Cogn Sci 8(9):418–425

Sporns O, Zwi JD (2004) The small world of the cerebral cortex. Neuroinformatics 2(2):145–162

Stam CJ (2010) Characterization of anatomical and functional connectivity in the brain: a complex networks perspective. Int J Psychophysiol 77(3):186–194

Stam CJ, Dijk BWv (2002) Synchronization likelihood: an unbiased measure of generalized synchronization in multivariate data sets. Phys. D 163(3):236–251

Stam CJ, Jones BF, Nolte G, Breakspear M, Scheltens P (2007) Small-world networks and functional connectivity in Alzheimer's disease. Cereb Cortex 17(1):92–99

Stam CJ, Reijneveld JC (2007) Graph theoretical analysis of complex networks in the brain. Nonlinear Biomed Phys 1(1):3

Strogatz SH (2001) Exploring complex networks. Nature 410(6825):268–276

Tecchio F, Zappasodi F, Porcaro C, Barbati G, Assenza G, Salustri C, Rossini PM (2008) High-gamma band activity of primary hand cortical areas: a sensorimotor feedback efficiency index. Neuroimage 40(1):256–264

Waldert S, Preissl H, Demandt E, Braun C, Birbaumer N, Aertsen A, Mehring C (2008) Hand movement direction decoded from MEG and EEG. J Neurosci 28(4):1000–1008

Westlake KP, Nagarajan SS (2011) Functional connectivity in relation to motor performance and recovery after stroke. Front Syst Neurosci 5:8

Chapter 8
Cortical Connections to Motor Cortex and Their Modulation in Behavioural Tasks

Giacomo Koch

Abstract Cortico–cortical connections that reach the primary motor cortex (M1) are thought to transmit crucial information relevant to build the final motor output required to perform a selected motor plan. These connections originate from key areas of the parietal and frontal lobes, such as the posterior parietal cortex (PPC), the supplementary motor area (SMA) and the ventral (PMv) and dorsal premotor cortex (PMd). Multifocal transcranial magnetic stimulation (TMS) has been recently investigated as a powerful method able to track within millisecond time scale direct information on the causal functional connectivity of these non-primary motor areas with the M1 that would explain how their activity may modulate the spatial pattern of output from primary motor areas preceding execution of a movement. A conditioning stimulus (CS) is first used to activate putative pathways to the motor cortex from, for example, the PPC or the PMd, while a second, test stimulus (TS), delivered over the M1 a few milliseconds later probes any changes in excitability that are produced by the CS. When tested at rest, the activation of these cortico–cortical projections may induce both a transient facilitation and a inhibition in the M1 ipsilateral or contralateral to the site of conditioning. However these interactions are not fixed, but may change critically during a certain motor task, giving important information on how the strength of the connection changes over time and during a specific task, and providing crucial information on the causal effects that a specific cortical region exerts over the M1. Moreover, it is possible to combine these measurements of functional connectivity together with diffusion tensor magnetic resonance imaging (DTI) to obtain insight into the white

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matter pathways that mediate these interactions. Here, we review studies describing the functional role of parallel cortico–cortical connections among the PMd, PMv, PPC and M1 in specific motor tasks such as action selection, action reprogramming, action observation and goal- directed reaching and grasping movements, showing that the functional interplay between these areas is not fixed, but is promptly activated depending on the behavioural state.

8.1 Introduction

Cortico–cortical connections that reach the primary motor cortex are thought to transmit crucial information relevant to build the final motor output required to perform a selected motor plan. For instance, reaching and grasping a cup to drink a coffee seems to be almost an automatic process, but the final successful performance requires a complex interaction of specific frontal and parietal brain networks to produce the optimum combination of arm and hand movement to manipulate the object most efficiently (Jeannerod et al. 1995). Classically, this type of action is supposed to involve cortical interconnected circuits including the parietal cortex, the premotor cortex and the primary motor cortex (Rizzolatti and Luppino 2001). Experiments in monkeys have shown that the inferior parietal lobule (IPL) contains a rich variety of neurons that discharge in association with reaching and grasping movements directed to specific goals (Sakata et al. 1995; Murata et al. 2000). It has been postulated that the different subregions of the IPL supply PMv with visual information on the attributes of objects (e.g., size, orientation) that are needed to select appropriate grasp configurations (Murata et al. 1997; Rizzolatti and Luppino 2001). Such information would eventually converge onto primary motor cortex (M1) for execution of the final motor plan (Rizzolatti and Luppino 2001; Shimazu et al. 2004; Prabhu et al. 2009).

In other situations, one should be able to quickly select, which hand has to move following a specific cue, such as when we have to plan sequence of movements that involve both hands (i.e. preparing, and not drinking, a coffee). In this case, single neuron recording and human neuroimaging studies indicate that the premotor cortex has an important role in the selection of movements for execution. Different parts of the premotor cortex may be related to the selection of different types of movement (Crammond and Kalaska 1996; Rizzolatti and Luppino 2001). The PMd seems to be involved particularly in the selection of movements according to learned arbitrary associations (Rushworth et al. 2003), in contrast to the ventral premotor areas that are involved in grasping movements triggered by viewing natural objects and body parts. Dum and Strick (2005) recently showed that M1, the PMd and the PMv form a dense ipsilateral interconnected network in which the direction of information flow is as likely to be from M1 to the premotor areas as it is from the premotor areas to M1.

While these studies reveal the contribution of the ventral (PMv) and dorsal premotor cortex (PMd) and aIPS in generating specific movements, *they do not provide direct information about the functional connectivity of these non primary motor areas with the primary motor cortex* that would explain how their activity may modulate the spatial pattern of output from primary motor areas preceding execution of a movement. *Yet, important and complementary information can be obtained by studying the physiology of the interactions occurring between the brain regions that form part of this cortical network* (Koch and Rothwell 2009). Previous combined TMS/PET and TMS/fMRI investigations have shown that transcranial magnetic stimulation (TMS) not only changes neural activity at the site of stimulation, but also affects interconnected cortical and sub-cortical areas (O'Shea et al. 2007a; Bestmann et al. 2008; Strafella et al. 2003). This feature has allowed paired pulse TMS with two coils (bifocal or twin-coil TMS) to probe inputs to the primary motor cortex from other areas of the motor system.

In these paradigms, a conditioning stimulus (CS) is first used to activate putative pathways to the motor cortex from the site of stimulation, while a second, test stimulus (TS), delivered over the primary motor cortex a few milliseconds later probes the changes in excitability that are produced by the input. Depending on the intensity of the conditioning stimulus and the interstimulus interval, both facilitation and inhibition may be detected in the M1, ipsilateral or contralateral to the site of conditioning. Previous studies have been conducted with the CS delivered over the contralateral M1 (Ferbert et al. 1992), the cerebellum, the premotor cortex (Civardi et al. 2001; Mochizuki et al. 2004; Bäumer et al. 2006) and the posterior parietal cortex (Koch et al. 2007, 2008a, b, 2009) confirming the existence of pathways from these areas to M1 in humans. For instance, Mochizuki et al. (2004) found that a conditioning TMS pulse over the right PMd at 90 or 110 % of the resting motor threshold (RMT) reduced the amplitude of motor evoked potentials (MEPs) in hand muscles elicited by a second TMS pulse to the contralateral M1. The effect was seen best if the interstimulus interval (ISI) was 8–10 ms. The opposite effect, facilitation of contralateral MEPs, was found by Bäumer et al. when they applied left PMd conditioning stimuli of lower intensity (80 % active motor threshold (AMT)) at ISI = 8 ms (Bäumer et al. 2006). The advantage of probing these pathways with TMS methods is that the response to a TMS conditioning pulse depends on the excitability of the pathway at the time the stimulus is applied. Thus, changes in the effectiveness of the conditioning pulse give an indication of how the excitability of the connection changes over time when the cortical networks become active during a specific motor task.

8.2 Functional Connectivity of Premotor-Motor Connections in Action Selection

In a recent study, we used these methods to test both the inhibitory and facilitatory connections between the PMd and contralateral M1 during a behavioural task requiring selection of action (Koch et al. 2006). We hypothesised that if they were *physiologically relevant* they would show *temporally specific changes in their excitability* at times when PMd contributes to task performance. In fact, previous studies showed that the PMd in the left hemisphere is dominant for selection of actions (Schluter et al. 2001; Rushworth et al. 2003), since the right PMd is active only for movements made by the left hand, whereas the left PMd is active for movements of either hand (Schluter et al. 2001). Furthermore, TMS of the right PMd only disrupts the selection of left hand movements, whereas TMS of the left PMd disrupts the selection of movements that will be made by either hand (Schluter et al. 1998). In both cases, TMS had the largest effect on performance if it was applied in the earlier part of the task, in contrast, with the disruptive effect of TMS over the M1 which is maximally late in the reaction period. Thus, activity in the PMd seems crucial during early decisional processes involved in selection of movements. In the study by Koch et al. (2006), subjects were required to contract the right or left first dorsal interosseus (FDI) muscle as quickly as possible, performing a rapid isometric squeeze of the block of the left or the right hand as soon they heard a cue sound (auditory choice RT task). The facilitatory and inhibitory PMd-M1 interactions were tested 50, 75, 100, 125, 150 and 200 ms after the cue sound (see Fig. 8.1a, b).

Koch et al. (2006) demonstrated that the interhemispheric interactions between left PMd and right M1 changed their excitability during the reaction period of the task. Facilitatory connections were activated 75 ms after a tone that indicated subjects should move the left hand, whereas inhibitory connections were more excitable 100 ms after a tone indicating a movement of the right hand (while the left hand remained stationary). These connections were modulated only for muscles that might be involved in the upcoming movement; no effects are observed in non-involved muscles. In contrast, results obtained from right PMd conditioning left M1 were slightly different, since the interhemispheric interactions between right PMd and left M1 at rest were mainly inhibitory and a similar profile of transcallosal inhibition as for left PMd-right M1 interactions was observed during the reaction period of the task, but no facilitation was evident at any time (see Fig. 8.1c, d). The authors suggested that the contribution of PMd to control of movements of the ipsilateral hand is due at least in part to activity in these pathways: *the left but not right PMd may facilitate movements that are about to be made by the ipsilateral hand, while the PMd of both hemispheres may suppress movements that have been prepared but are not used.*

Similar results were obtained by O'Shea et al. (2007b), in a study testing PMd-M1 inter-hemispheric interaction during action selection with visual cues. PMd-M1 TMS facilitated MEPs when applied 75 ms after a cue to select a manual response, confirming that a response selection signal evolves in PMd early during the reaction period (75–100 ms).

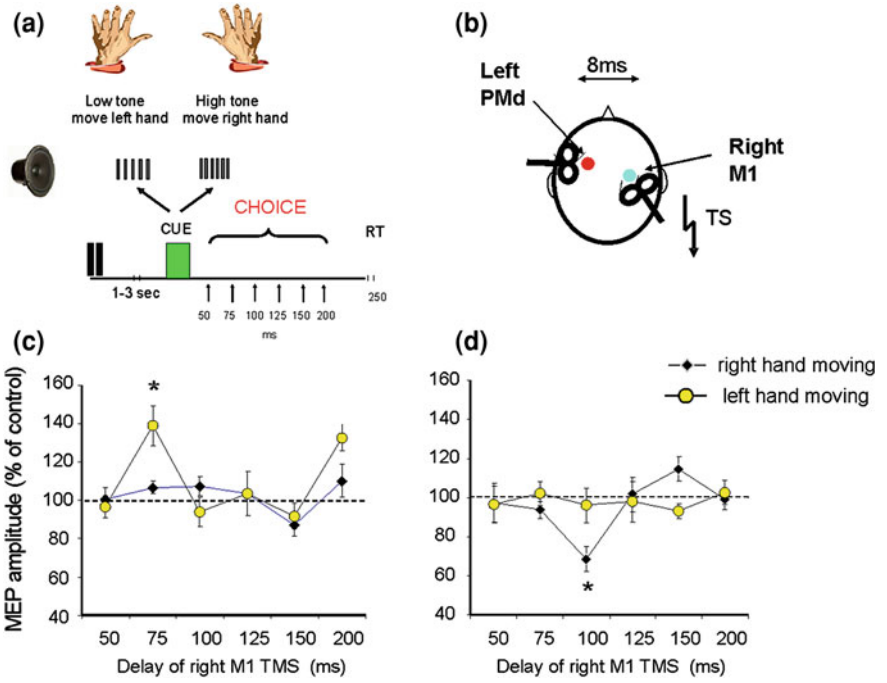

Fig. 8.1 Functional connectivity between PMd and contralateral M1 during movement selection. **a** Schematic representation of the choice reaction time task. Subjects were required to activate right or left FDI muscle as quickly as possible, performing a rapid isometric contraction of either hand as soon they hear a cue sound. TMS was delivered over left or right M1 at different delays (50, 75, 100, 125, 150 and 200 ms) after the cue sound (test stimulus-TS). The intensity of TS was adjusted to evoke an MEP of approximately 1 mV peak-to-peak in the relaxed left FDI. In half of the trials M1 TMS was preceded by a conditioning stimulus (CS) delivered 8 ms before over the contralateral PMd (**b**). Facilitatory connections (**c**) were evident 75 ms after a tone that indicates subjects should move the left hand, whereas inhibitory connections (**d**) manifested 100 ms after a tone indicating a movement of the right hand. Methods and results adapted from Koch et al. (2006)

8.3 Functional Connectivity of Premotor-Motor Connections in Action Reprogramming

A recent series of experiments investigated the functional role of the premotor–motor connections during action reprogramming. In particular, these studies were focused in circuits involving the pre-supplementary motor area (pre-SMA), the PMv and the M1. Using bifocal TMS, Mars et al. (2009) investigated functional connectivity between the pre-SMA and M1. The task required participants to either execute a prepared response or switch to another response. A test TMS pulse was delivered over left M1. On some trials it was preceded by a conditioning pulse over pre-SMA.

Mars et al. (2009) found that functional connectivity increased in a manner dependent on cognitive context: pre-SMA facilitated the MEP elicited by M1 stimulation only during action reprogramming, but not when otherwise identical actions were made in the absence of conflict. The results showed that pre-SMA influences corticospinal excitability at a short latency of 6 ms. The effect was evident 125 ms after movement instruction was anatomically specific to pre-SMA, and occurred only during action reprogramming.

In another study, bifocal TMS was used to examine functional interactions between human right PMv and contralateral M1 during the selection and reprogramming of a naturalistic goal-directed action (Buch et al. 2009). One of two cylinders was illuminated on each trial. It was then grasped and picked up. On some trials, however, subjects had to reprogram the action as the illuminated cylinder was switched off and the other illuminated simultaneously with reach initiation. At a neurophysiological level, the PMv effect on the M1 corticospinal activity, was facilitatory after the initial target presentation and during movement initiation. When reprogramming was required, however, it became strongly inhibitory. This context-dependent change from facilitation to inhibition occurred within 75–100 ms of the change of target (Buch et al. 2009). An attempt was also made to assess the impact this inhibitory physiological effect had on behavior. Indeed, the application of PMv-M1 TMS at the ISI of 75 ms caused a specific delay in grasp aperture adjustments on small to large cylinder switch trials. Although the applied stimulation was not optimised to disrupt performance, it still caused a reduction in grasp aperture adjustments measured at the midpoint of the movement on switch trials. The authors suggested that, under circumstances where reprogramming is required, PMv generates a specific pattern of inhibition across M1 that leads to decreased activity in M1 corticospinal neurons associated with the initial movement.

Finally, magnetic resonance image scans were taken of each subject

Notably, it is possible to use diffusion tensor magnetic resonance imaging (DTI) to obtain some insight into the white matter pathways that connect these areas in humans. DTI can reconstruct in vivo white matter fibre bundles based on the assumption that the principal direction of tissue water diffusion is parallel to the main fibre direction in every voxel. Moreover, the orientation dependence of diffusion can then be quantified by fractional anisotropy (FA) at each voxel. Other authors have found an association between FA DTI values in certain white matter tracts and measures of functional connectivity as measured by TMS. They suggest that this increases the confidence that the physiological interactions observed were produced by activity in that specific tract (Wahl et al. 2007; Boorman et al. 2007; Mars et al. 2009; Koch et al. 2011). Intersubject differences in the facilitation–inhibition contrast of PMv-M1 interactions were correlated with FA of white matter in ventral prefrontal, premotor and intraparietal brain areas, with the largest clusters emerging in the vicinity of PFv and IPS in the right hemisphere.

Neubert et al. (2010) used a combination of techniques to characterise the interaction among different cortical regions during action reprogramming and to study the underlying anatomical networks involved. They first used bifocal TMS to

characterise the interactions between rIFG and pre-SMA with M1 during normal action selection and action reprogramming. Whereas pre-SMA, on switch trials, facilitates the unexpected and unprepared but correct response 125 ms after instruction cue onset, rIFG inhibits the prematurely activated but incorrect response 175 ms after cue onset. Then, they used a combination of ppTMS and diffusion-weighted (DW) MRI to investigate the anatomical networks that support these interactions. TMS was delivered at the postvisual cue time point of maximum interaction (125 for pre-SMA-M1 and 175 ms for rIFG-M1) with variable interpulse latencies (IPLs = 3, 6, 9, 12 and 18 ms). To relate patterns of functional connectivity to the anatomical white matter tracts by which they were mediated, the authors correlated individual differences in ppTMS effect sizes with individual differences in DTI-derived FA, to localise pathways mediating interactions between pre- SMA/M1 and rIFG/M1 connectivity during action reprogramming within the white matter. The results showed that the clusters significantly correlated with TMS effects in the pre-SMA/M1 experiment with an IPL of 6 ms generated tracts within dorsomedial frontal and parietal white matter connecting pre-SMA and premotor areas with motor and parietal areas. However, tracts derived from clusters significantly correlated with TMS effects in the pre-SMA/M1 experimentwith an IPL of 12 ms connected pre-SMA with ventral and dorsal premotor areas; areas in the rIFG, M1, and parietal areas; and subcortical areas in the vicinity of the subthalamic nucleus (STN), suggesting that longer latency pathways might be mediated by the basal ganglia, including the STN. This is important because it has been argued that STN is a particularly critical part of the circuit for action inhibition and that a pathway running from the striatum via the globus pallidus and STN might be critical for learning when to withhold actions that are unrelated to reward.

8.4 Functional Connectivity of Premotor-Motor and Parietal-Motor Connections in Planning of Reaching and Grasping Movements

In a recent study, Davare et al. (2008) investigated PMv-M1 connections and compared whether they were differentially modulated at rest, and during grasping. The subjects had to perform either a precision grip (grasping a 20 mm plasticine cube between the thumb and index finger) or a power grip (grasping a tennis ball). TMS was applied over M1 either alone or after a CS delivered at different delays over the ipsilateral PMv. The results showed that at rest, PMv exerts an inhibitory influence on M1, as reflected in the suppression of MEPs evoked from M1 by TMS. This interaction was selectively modulated during different types of grasp. During power grip, inhibition was reduced while during precision grip—a task known to be associated with a particularly strong activation of PMv (Ehrsson et al. 2000)—it turned into facilitation. *These results suggest a causal role of PMv-M1*

interactions in precision grasping and support the view that connections between PMv and M1 could be critically involved in conveying information used to adapt hand posture appropriate for the object to be grasped (Shimazu et al. 2004).

In another study, the same authors investigated PMv-M1 interactions while subjects were preparing to grasp different visible objects requiring either a precision grip or a whole hand grasp (Davare et al. 2009). While subjects prepared to grasp, delivering a conditioning PMv pulse few milliseconds before a test pulse over M1 strikingly facilitated MEPs in the specific muscles that were used in the upcoming grasp. This degree of facilitation correlated with the amount of muscle activity used later in the trial to grasp the objects. The present results demonstrate that, during grasp preparation, the PMv-M1 interactions are muscle specific. The authors argued that PMv appears to process the object geometrical properties relevant for the upcoming grasp, and transmits this information to M1, which, in turn, generates a motor command appropriate for the grasp.

Indeed, in a following related study, Davare et al. (2010) tested how PMv-M1 interactions and were modified by disrupting anterior intraparietal cortex (AIP) function with continuous theta burst stimulation (cTBS). At rest, AIP virtual lesions did not modify PMv-M1 interactions. In contrast, the usual muscle-specific PMv-M1 interactions that appeared during grasp preparation were significantly reduced following AIP cTBS without directly modifying corticospinal excitability. Behaviourally, disruption of AIP was also associated with a relative loss of the grasp specific pattern of digit muscle activity. These findings showed that *disruption of AIP impairs the normal changes in task-related interactions between PMv and M1* that prepare the hand muscles to grasp an object, suggesting that AIP is critical in processing context- and grasp-dependent information, which enables PMv to bias excitability levels in M1 hand representation during the preparation for an upcoming grasp.

We recently developed a new method for investigating functional connections between the posterior parietal cortex and ipsilateral motor cortex non-invasively in humans, using a twin-coil or bifocal TMS paradigm (Koch et al. 2007). In this method, a conditioning TMS pulse is applied over PPC shortly before a test pulse over the hand area of M1. At rest, stimulation of the angular gyrus (AG) close to the caudal intraparietal sulcus (cIPS) at specific intensities can facilitate ipsilateral M1 while stimulation of the supramarginal gyrus (SMG) close to the anterior portion of the IPS (aIPS) leads to suppression (Koch et al. 2007). In recent experiments we tested how this connectivity depends on current motor plans, applying TMS not only at rest, but also during the reaction time of a task requiring reaching movements toward a left or right visual target (Koch et al. 2008a) (see Fig. 8.2a, b). The results showed that the excitability of cortico–cortical connections between AG and M1 change at specific times during planning of reaching movements in space (see Fig. 8.2c). After an auditory warning cue, subjects were instructed to fixate a cross positioned in the middle of a panel. The reaction signals were given randomly 1–3 s later and consisted of either a high or low frequency tone pulse that indicated where to reach, according to the instructions given to the

subjects. Upon hearing the sound, subjects were required to point to a peripheral target positioned in the left or right hemispace. To obtain the best activation of the parieto-motor cortico–cortical interaction (Koch et al. 2007), a CS was delivered over the ipsilateral cIPS at an intensity of 90 % RMT. After 4 ms a TS was applied over the hand motor cortex with an intensity able to evoke MEP of approximately 1 mV peak-to-peak in the relaxed left FDI.

The same paired-pulse TMS during the planning phase of our reach task *revealed facilitatory influences only when planning a leftward but not a rightward reach*, at two specific time intervals after the auditory cue. The first phase occurred 50 ms after the acoustic cue, and was seen independently of whether subjects were able to view the targets (see Fig. 8.2c). This phase of facilitation was followed by a later peak at 125 ms that only occurred when subjects were able to see the target but was absent when blindfolded or when they could see the stimuli only briefly. The dependence of our later PPC-M1 facilitatory effect on vision of target locations may reflect a recursive cycle, in which initial motor intentions then lead to reliance on visual information (Prado et al. 2005; Clavagnier et al. 2007). Availability of visual input at this later stage of processing may be used by PPC-M1 circuits to define the exact location of the peripheral visual target more precisely. This could accord with the general idea that PPC is important for integrating visual and motor information. More specifically, we proposed that the early peak of PPC-M1 facilitation at 50 ms may reflect initial biasing of motor intentions toward contralateral space, whereas the later peak at 125 ms that depends on visual input may contribute to the spatial accuracy of motor planning (Koch et al. 2008a). Therefore, we concluded that functional connectivity between human parietal and motor cortex is enhanced during early stages of planning a reach in the contralateral direction (Koch et al. 2008a). It appeared that information on the location of the target was being sent to M1 very early in the reaction period of the task. *In classical terms this could therefore be viewed as contributing to the reaching component of the task.*

The previous task involved subjects reaching and pointing to the target with their index finger. In a recent study, we used the same methods to investigate the contribution of different subregions of the IPL, such as the more posterior AG and the more anterior SMG, in planning of reaching and grasping actions. We studied whether the interaction between these regions of the IPL in the left hemisphere and the ipsilateral M1 would change when subjects were planning to reach and grasp a single object in two different ways: a precision grip (PG) and whole hand grasp (WHG). We decided to test the left hemisphere since these movements in everyday life are performed with the dominant right hand. We also varied the position of the object in space in order to test for specific reaching spatial components of the task (Koch et al. 2008a). We hypothesised that the AG-M1 connection would be involved in programming the upcoming grasp when the target object has to be reached by a lateral movement (Castiello 2005; Karnath and Perenin 2005). On the other hand, we predicted that the SMG-M1 connection would be involved in

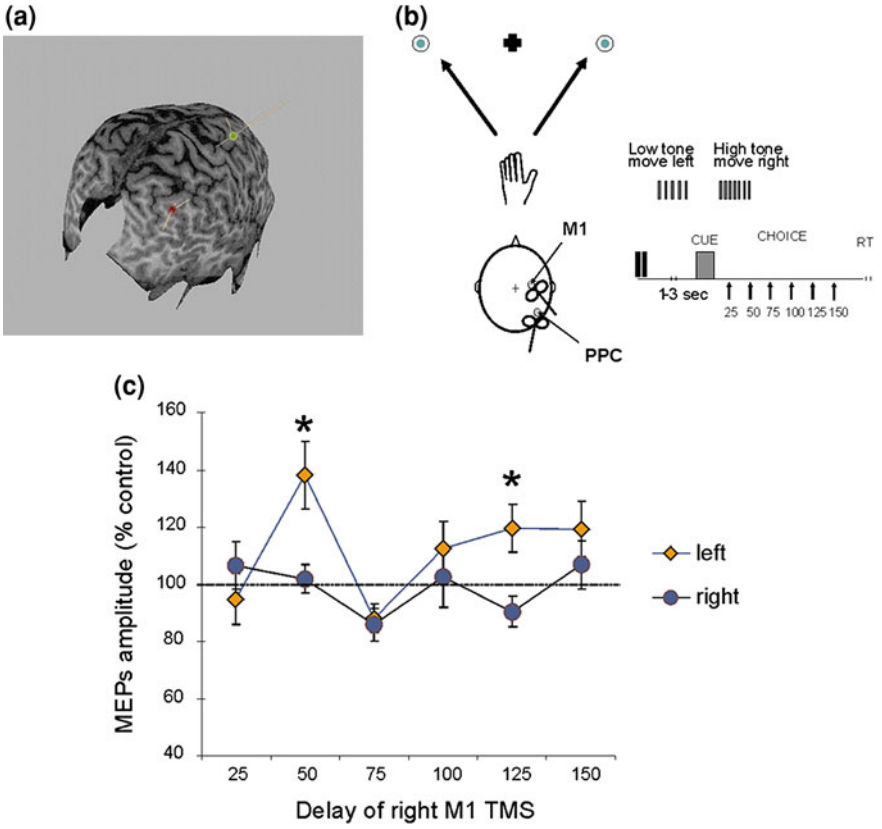

Fig. 8.2 Functional connectivity between PPC and ipsilateral M1 during preparation of ipsilateral or contralateral reaching movements. **a** Conditioning TMS stimulus was applied at 90 % of RMT over posterior parietal cortex (PPC) at a site corresponding to the AG near the caudal intraparietal sulcus (cIPS). **b** Schematic representation of the reaching task. At trial onset subjects fixated the central cross. After the imperative cue sound (occurring randomly 1–3 s later), they reached to the left or right target with their left hand. TMS was delivered over M1 of the right hemisphere at different delays (25, 50, 75, 100, 125 and 150 ms) after the cue sound onset, and thus prior to actual reach initiation. In half of the trials, M1 TMS was preceded 4 ms earlier by a PPC TMS pulse (intensity = 90 %RMT). **c** Effects of PPC conditioning on ipsilateral M1 excitability at different delays after the cue signal, when subjects planned left hand reaches to visible targets on left or right. The mean percentages of baseline MEP amplitude due to right PPC conditioning are shown in panel C, with 100 % representing no change. Cortico–cortical PPC-M1 facilitation occurred selectively at an early delay of 50 ms and at the later point of 125 ms after the auditory imperative cue for a leftward reach (yellow points in C). There was no facilitation when a rightward reach was planned (dark points in C). Methods and results adapted from Koch et al. (2007)

specifying specific parameters for grasp (i.e., WHG vs. PG) rather than reach, given that the SMG can be considered part of the homologue region of the AIP described in monkeys (Sakata et al. 1995; Murata et al. 2000; Binkofski et al. 1998; Culham and Valyear 2006; Olivier et al. 2007; Begliomini et al. 2007).

We used an auditory choice RT task similar to that previously described by Koch et al. (2008a) but adapted to emphasise reaching to grasp movements according to our experimental hypotheses about PPC–M1 influences. The task was to reach, grasp and lift with the right hand a cup located on a central or right lateral position (targets visible throughout the experiment), as signalled by an auditory tone, indicating symbolically how the subject should have grasped on that particular trial (see Fig. 8.3a). Depending on the tone, subjects were required either to pinch the handle of the cup (precision grip-PG) or to grasp the whole cup from the top (whole hand grasp-WHG). We examined the excitability of the AG-M1 and SMG-M1 interactions in the reaction interval between the onset of the auditory signal and the start of the grasping movement. Since no arm or hand movement occurs in this period, the TMS responses are not contaminated by ongoing EMG activity in the hand muscles. Bifocal TMS experiments revealed that in the left hemisphere functional connectivity between the AG and the M1 was activated during early preparation of reaching and grasping movements only when the movement was made with a WHG toward objects in contralateral space. Cortico–cortical AG–M1facilitation occurred selectively at an early delay of 50 ms after the auditory imperative signal for a rightward WHG for both the FDI and the ADM muscles (Koch et al. 2010a) (see Fig. 8.3b). In our previous study (Koch et al. 2008a) we found that the excitability of the interaction between AG and M1 was modulated during the reaction period when subjects had to point to a target positioned in contralateral space, but not if the target was in the midline. We showed that this modulation is still present when subjects have to pick up an object (cup), but only when they use a whole hand grip (WHG). If they are instructed to use a PG then there is no change in excitability in the reaction period. We interpreted this change *as reflecting an early biasing of movement plans in the contralateral direction that is specific for the WHG task*. In effect, this connection appears to process information relevant to both object position and grasp type. Thus, the effect of object position observed for the AG–M1 connection may indicate that this pathway is sensitive to the reach component of WHG task (Koch et al. 2008a).

In contrast, a different pathway, linking a part of the SMG close to the anterior intraparietal sulcus with M1, was sensitive only to the type of grasp required (precision grasping) but not to the position of the object in space. These results for the SMG–M1 interaction were quite different: *it was modulated by grasp type but not by position of the object* (Koch et al. 2010a). This occurred at different delays from the acoustic cue in comparison with AG stimulation. In reaching to the central target, there was a specific peak of facilitation for the M1 output to FDI some 75–100 ms after the imperative signal, but only if this instructed subjects to use a PG. There was no effect if a WHG was specified (see Fig. 8.3c). These results were similar when subjects were grasping the laterally placed object except that the facilitation for PG was observed at 125 ms after the cue. We interpreted this change in excitability of SMG to M1 as reflecting a transfer of information that is relevant to prepare activation of those hand muscles needed to perform

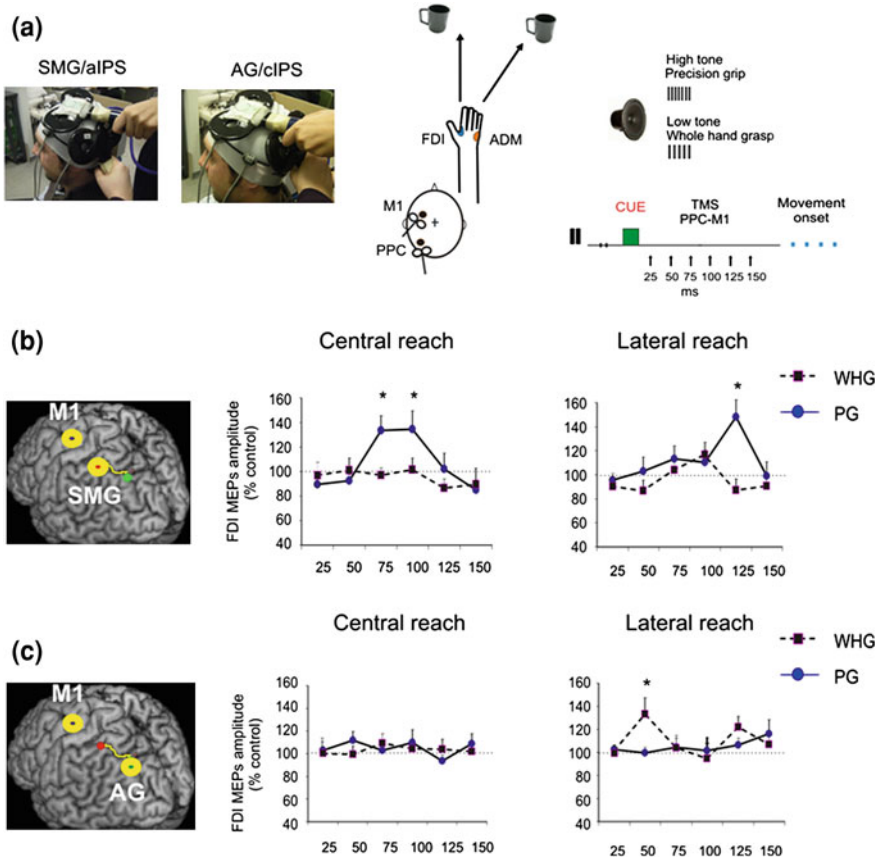

Fig. 8.3 Schematic representation of bifocal TMS coils placement and recordings during the planning phase of the reaching to grasp task (**a**). In different experiments a conditioning stimulus was applied over sub-regions of the PPC (AG and SMG), preceding by 4 ms in half of the trails the test stimulus delivered over M1. Motor evoked potentials were recorded by the FDI and the abductor digiti minimi (ADM) muscles. Depending on an acoustic cue, subjects were required to perform either a precision grip or a whole hand grasp of a cup positioned in different blocks centrally or laterally on the side opposite of the stimulated hemisphere. The effects of AG conditioning on ipsilateral M1 excitability at different delays after the cue signal, when subjects planned right hand reaches to grasp the cup are shown in panels B and C. Panels show mean percentage of MEP amplitudes (with 100 % representing no change) due to left AG conditioning recorded from the right FDI at different time points after the imperative auditory signal, when central or rightward PG or WHG movements were planned. **b** Cortico–cortical AG-M1 facilitation occurred selectively at an early delay of 50 ms after the auditory imperative signal for a rightward WHG for both muscles. **c** Cortico–cortical SMG-M1facilitation occurred selectively during central PG and not WHG for the FDI muscle at delays of 75 and 100 after the auditory imperative signal and again at 125 ms for a rightward PG. Methods and results adapted from Koch et al. (2010b)

precise grasping movements. This interpretation is in line with studies in patients with circumscribed lesions of the anterior part of the PPC who have deficits in hand pre-shaping during visually guided reach-to-grasp movements (with a relative preservation of reaching) (Binkofski et al. 1998) and also with the hypothesis that these regions may represent the human homologue of AIP (Culham and Valyear 2006). These results are also consistent with recent fMRI investigations, revealing that the left SMG is active when subjects perform a PG to reach and grasp a small object, with a negligible activity for WHG (Begliomini et al. 2007). They are also in agreement with the idea that planning an accurate and precise movement, such as PG, requires activity in a dorso-lateral circuit, which includes the SMG but not the AG (Grol et al. 2007). Finally, these results may reflect previous findings from animal studies, reporting that the neural coding of goal-directed actions (i.e., grasping for eating and grasping for placing) is mainly represented in the AIP (Murata et al. 2000).

Crucially, motor cortex excitability did not vary over the same period, suggesting that the modifications in PPC–M1 connectivity reflect changes in the excitability of the stimulated regions (SMG or AG) rather than M1 itself.

Previous animal data suggest that both AG and SMG have strong connections with PMv, where neurons with similar functions have also been identified (Rozzi et al. 2006). Since PMv has powerful connections with M1 (Shimazu et al. 2004; Prabhu et al. 2009; Davare et al. 2008), we therefore asked whether the functional effects that we had observed in the twin-coil TMS experiments would be affected by a temporary interference with the function of PMv produced by a short period of repetitive TMS. When cTBS was applied over the left PMv, the task related PPC–M1 connectivity changes were substantially reduced. In particular, the peak of facilitation observed following AG stimulation during planning of lateral WHG at 50 ms disappeared. Similarly, the increase of excitability at 75 ms, which occurred following AG stimulation during the reaction period of a central PG, was abolished (Koch et al. 2010a).

Taken together, these results imply that the *left PMv can be a crucial node in the neural network linking AG and SMG with the ipsilateral M1*. Therefore, we may speculate that activation of cortico–cortical projections originating from AG to SMG may synapse with neurons of the ipsilateral PMv or at least be influenced by input from that structure.

Although bifocal TMS can provide reliable measures of the causal functional interactions between the two areas (Koch and Rothwell 2009), it does not provide any information on the possible anatomical pathways that might mediate the responses. DTI tractography experiments (Koch et al. 2010a) revealed that *AG and SMG are connected with PMv by distinct fibres bundles of the superior longitudinal fasciculus (SLF)*, likely corresponding to the SLF II (fibres form AG) and SLF III (fibres from SMG) subdivisions (Makris et al. 2005). Analysis of the strength of connectivity suggests that the SMG and AG are more likely to be directly connected to PMv than M1. In fact, sparse direct connections between AG and SMG to M1 were found (see Fig. 8.4). These findings are in agreement with previous anatomical studies performed in monkeys (Rozzi et al. 2006), showing

that most of the fibres originating from inferior parietal lobule, that form part of the SLF, terminate in PMv (F5). In contrast, direct prominent anatomical connections between the posterior parietal cortex and M1 have been described only for the superior parietal lobule (area PE) (Matelli et al. 1998; Marconi et al. 2001). We also found correlations between individual TMS and the strength of connectivity (SoC) measures. There was a positive correlation between SoC of the SMG-PMv tract and the amount of facilitation for the SMG-M1 interaction during planning of PG; similarly, there was a positive correlation between the SoC of the AG-PMv tract and the amount of facilitation for the AG-M1 interaction observed during preparation of lateral WHG (see Fig. 8.4). These data seem to suggest that subjects which have stronger anatomical representation of a certain white matter tract may also have stronger neurophysiological interactions, supporting the notion that the observed neurophysiological changes might be mediated by the anatomical pathways reconstructed by DTI analysis (Koch et al. 2010a).

8.5 Functional Connectivity of Premotor-Motor and Parietal-Motor Connections During the Observation of Reaching and Grasping Movements

Finally, recent studies investigated these cortico–cortical circuits not only during movement preparation but also during movement observation. In monkeys, neurons of these areas become active also during the observation of movements performed by others, especially for coding the goal of the action (mirror system) (Rizzolatti et al. 2009). Using bifocal TMS in healthy subjects, Koch et al. (2010b) tested whether the observation of goal directed reach-to-grasp actions may lead to specific changes in the short-latency connections linking key areas of the mirror system, such as the AIP and the PMv, with the M1. The authors found that AIP-M1 and PMv-M1 cortico–cortical interactions were specifically activated when observing successful reaching to grasp goal-directed actions, *in which the hand posture was congruent with the goal of the action performed by the actor*. On the other hand, they were not modified when the same goal-directed actions were performed wrongly with an inappropriate grasping posture. The current results demonstrate that, in humans, the simple observation of successful goal-directed actions is sufficient to activate short-latency cortico–cortical connections between non-primary and primary motor areas. The excitability of cortico–cortical pathways originating from key areas of the mirror system, such as the AIP and PMv, does not simply change in response to the observation of a specific hand posture, but increases selectively only when both the hand posture and the goal of the action performed by the actor are congruent. Furthermore, a similar profile of activation was observed when testing a specific facilitatory intracortical circuit in M1 that is known to reflect the activity in cortico–cortical pathways transmitting

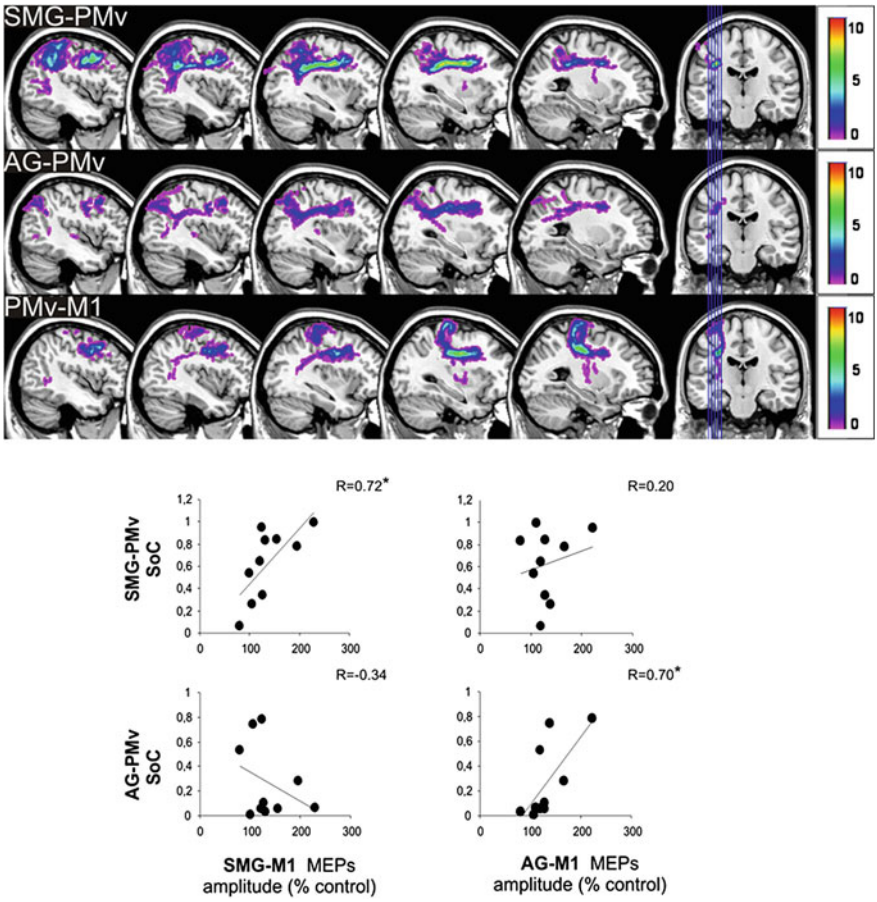

Fig. 8.4 The three main pathways connecting the IPS, PMv and M1 are shown in the figure, by means of the overlap between subjects. The SMG-PMv connection (top panel) the AG to PMv (middle panel) and the PMv-M1 connection were successfully reconstructed in all subjects and show a relatively reproducible shape across individuals. Correlation analyses between individual MEPs facilitation induced by PPC stimulation and tracts specific SoC provided further evidence of the linkage between microstructure and function of these parieto-motor pathways. Changes in MEP amplitude induced by SMG stimulation (individual values for peak of facilitation at 100 ms delay during central PG preparation) correlated selectively with SoC of the SMG-PMv tract, but not with FA of other tracts; changes in connectivity due to AG stimulation (individual values for peak of facilitation at 50 ms delay during lateral WHG preparation) correlated with SoC of the AG-PMv tract but not with FA of the other tracts. Results adapted from Koch et al. (2010a)

information from other cortical areas. Taken together, these data demonstrate that observing others' actions induces specific neurophysiological changes in short-latency cortico–cortical circuits of the motor system.

Lago et al. (2010) evaluated the excitability of PMv–M1 connections during the observation of videos showing a human hand reaching to grasp a ball (naturalistic

grasping video) or a switched on soldering iron (noxious grasping video). The results showed that the observation of the naturalistic grasping action increased the M1 excitability and changed the strength of the PMv–M1 connections. The PMv–M1 facilitation was modulated during the observation of the video that displayed a hand reaching a ball. The facilitation found at the beginning of the video (when the hand was static) turned into inhibition at the moment of the grasp. The observation of a movement performed to grasp a noxious object did not induce any change in the excitability of the PMv–M1 connection throughout the video, even when the action and the kinematics of the hand observed in both reaching videos were identical. However, the strength of PMv–M1 connectivity was reduced compared to other conditions at the beginning of the video, when subjects were presented with the potentially noxious object. These findings demonstrate that the PMv–M1 connections are modulated differently depending on whether the action observed would or would not be performed in real life.

8.6 Conclusions

Multifocal TMS methods allow investigators to study the time course of involvement as well as the functional connectivity of areas active during preparation and execution of complex movement plans. They illustrate *the time course of operation of parallel intracortical circuits and cortico-cortical connections* between the PMd, PMv, PPC and M1, demonstrating that functional interplay between these areas and the primary motor cortices is not fixed, but can change in a highly task-, condition- and time-dependent manner (see Fig. 8.5). These information is particularly useful to reveal the *causal interactions* ongoing between the two areas investigated with the paired-pulse technique, reflecting the activation of actual connections. Although the information detected by TMS reveals ongoing functional interactions with high-temporal resolution, it does not provide any specific anatomical detail on the white matter tracts supporting the neurophysiological measures. Combining twin-coil TMS with neuroimaging techniques such as DTI can be useful to obtain more complete anatomo-functional knowledge (i.e. Wahl et al. 2007; Boorman et al. 2007; Mars et al. 2009; Koch et al. 2011). Moreover, further studies could be made coupling such TMS methods with dynamic causal modelling (DCM), that allows to estimate effective connectivity in a stimulus-driven network using functional imaging data (Grefkes et al. 2002). Finally, functional connectivity between two cortical regions revealed by twin-coil TMS could also be explored following a virtual lesions of another network related area (as in Davare et al. 2010 and Koch et al. 2010a), in order to better investigate neurophysiologic interactions within complex interconnected networks.

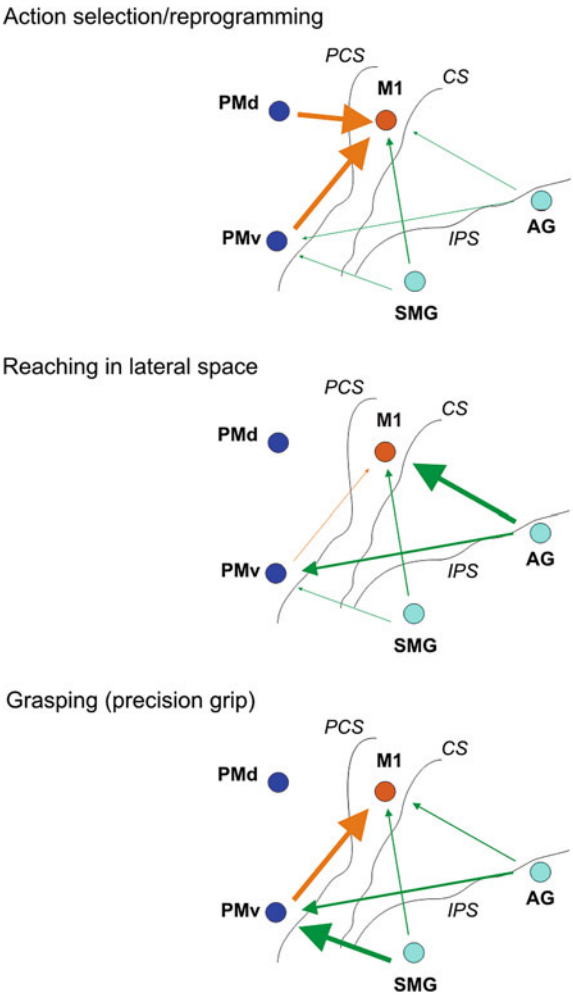

Fig. 8.5 Schematic representation of the activation of cortical inputs to M1 in different behavioural tasks as revealed by TMS studies. The size of the arrows indicates the specific activation of the cortico-cortical connection in a given behavioural task. IPS = intraparietal sulcus; CS = central sulcus; PCS = precentral sulcus

References

Basser PJ, Mattiello J, LeBihan D (1994) MR diffusion tensor spectroscopy and imaging. Biophys J 66:259–267

Bäumer T, Bock F, Koch G, Lange R, Rothwell JC, Siebner HR, Munchau A (2006) Magnetic stimulation of human premotor or motor cortex produces interhemispheric facilitation through distinct pathways. J Physiol (Lond) 572:857–868

Begliomini C, Wall MB, Smith AT, Castiello U (2007) Differential cortical activity for precision and whole-hand visually guided grasping in humans. Eur Neurosci 25:1245–1252

Bestmann S, Ruff CC, Blankenburg F, Weiskopf N, Driver J, Rothwell JC (2008) Mapping causal interregional influences with concurrent TMS-fMRI. Exp Brain Res 191:383–402

Binkofski F, Dohle C, Posse S, Stephan KM, Hefter H, Seitz RJ, Freund HJ (1998) Human anterior intraparietal area subserves prehension: a combined lesion and functional MRI activation study. Neurology 50:1253–1259

Boorman ED, O'Shea J, Sebastian C, Rushworth MF, Johansen-Berg H (2007) Individual differences in white-matter microstructure reflect variation in functional connectivity during choice. Curr Biol 17:1426–1431

Castiello U (2005) The neuroscience of grasping. Nat Rev Neurosci 6:726–736

Clavagnier S, Prado J, Kennedy H, Perenin MT (2007) How humans reach: distinct cortical systems for central and peripheral vision. Neuroscientist 13:22–27

Civardi C, Cantello R, Asselman P, Rothwell JC (2001) Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. Neuroimage 14:1444–1453

Crammond DJ, Kalaska JF (1996) Differential relation of discharge in primary motor cortex and premotor cortex to movements versus actively maintained postures during a reaching task. Exp Brain Res 108:45–61

Culham JC, Valyear KF (2006) Human parietal cortex in action. Curr Opin Neurobiol 16: 205–212

Davare M, Lemon R, Olivier E (2008) Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans. J Physiol 586:2735–2742

Davare M, Montague K, Olivier E, Rothwell JC, Lemon RN (2009) Ventral premotor to primary motor cortical interactions during object-driven grasp in humans. Cortex 45(9):1050–1057

Davare M, Rothwell JC, Lemon RN (2010) Causal connectivity between the human anterior intraparietal area and premotor cortex during grasp. Curr Biol 20(2):176–181

Dum RP, Strick PL (2005) Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. J Neurosci 25:1375–1386

Ehrsson HH, Fagergren A, Jonsson T, Westling G, Johansson RS, Forssberg H (2000) Cortical activity in precision- versus power-grip tasks: an fMRI study. J Neurophysiol 83:528–536

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. J Physiol 453:525–546

Grefkes PH, Weiss K, Zilles Fink GR (2002) Crossmodal processing of object features in human anterior intraparietal cortex: an fMRI study implies equivalencies between humans and monkeys. Neuron 35:173–184

Grol MJ, Majdandzić J, Stephan KE, Verhagen L, Dijkerman HC et al (2007) Parietofrontal connectivity during visually guided grasping. J Neurosci 27:11877–11887

Jeannerod M, Arbib MA, Rizzolatti G, Sakata H (1995) Grasping objects: the cortical mechanisms of visuomotor transformation. Trends Neurosci 18:314–320

Karnath HO, Perenin MT (2005) Cortical control of visually guided reaching: evidence from patients with optic ataxia. Cereb Cortex 15:1561–1569

Koch G, Franca M, Fernandez Del Olmo M, Cheeran B, Milton R, Alvarez Sauco M, Rothwell JC (2006) Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. J Neurosci 26:7452–7459

Koch G, Fernandez Del Olmo M, Cheeran B, Ruge D, Schippling S, Caltagirone C, Rothwell JC (2007) Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. J Neurosci 27:6815–6822

Koch G, Fernandez Del Olmo M, Cheeran B, Schippling S, Caltagirone C, Driver J, Rothwell JC (2008a) Functional interplay between posterior parietal and ipsilateral motor cortex revealed by twin-coil TMS during reach planning toward contralateral space. J Neurosci 28:5944–5953

Koch G, Oliveri M, Cheeran B, Ruge D, Lo Gerfo E, Salerno S, Torriero S, Marconi B, Mori F, Driver J, Rothwell JC, Caltagirone C (2008b) Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. Brain 131(Pt 12):3147–3155

Koch G, Ruge D, Cheeran B, Fernandez Del Olmo M, Pecchioli C, Marconi B, Versace V, Lo Gerfo E, Torriero S, Oliveri M, Caltagirone C, Rothwell JC (2009) TMS activation of interhemispheric pathways between the posterior parietal cortex and the contralateral motor cortex. J Physiol 587(Pt 17):4281–4292

Koch G, Rothwell JC (2009) TMS investigations into the task-dependent functional interplay between human posterior parietal and motor cortex. Behav Brain Res 202(2):147–152

Koch G, Cercignani M, Pecchioli C, Versace V, Oliveri M, Caltagirone C, Rothwell J, Bozzali M (2010a) In vivo definition of parieto-motor connections involved in planning of grasping movements. Neuroimage 51(1):300–312

Koch G, Versace V, Bonnì S, Lupo F, Lo Gerfo E, Oliveri M, Caltagirone C (2010b) Resonance of cortico-cortical connections of the motor system with the observation of goal directed grasping movements. Neuropsychologia 48:3513–3520

Koch G, Cercignani M, Bonnì S, Giacobbe V, Bucchi G, Versace V, Caltagirone C, Bozzali M (2011) Asymmetry of parietal interhemispheric connections in humans. J Neurosci 31(24):8967–8975

Lago A, Koch G, Cheeran B, Márquez G, Sánchez JA, Ezquerro M, Giraldez M, Fernández-del-Olmo M (2010) Ventral premotor to primary motor cortical interactions during noxious and naturalistic action observation. Neuropsychologia 48:1802–1806

Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, Pandya DN (2005) Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. Cereb Cortex 15:854–869

Mars RB, Klein MC, Neubert FX, Olivier E, Buch ER, Boorman ED, Rushworth MF (2009) Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. J Neurosci 29:6926–6931

Matelli M, Govoni P, Galletti C, Kutz DF, Luppino G (1998) Superior area 6 afferents from the superior parietal lobule in the macaque monkey. J Comp Neurol 402:327–352

Mattingley JB, Husain M, Rorden C, Kennard C, Driver J (1998) Motor role of human inferior parietal lobe revealed in unilateral neglect patients. Nature 392:179–182

Mochizuki H, Huang YZ, Rothwell JC (2004) Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. J Physiol 561:331–338

Murata A, Gallese V, Luppino G, Kaseda M, Sakata H (2000) Selectivity for the shape, size, and orientation of objects for grasping in neurons of monkey parietal area AIP. J Neurophysiol 83:2580–2601

Murata A, Fadiga L, Fogassi L, Gallese V, Raos V, Rizzolatti G (1997) Object representation in the ventral premotor cortex (area F5) of the monkey. J Neurophysiol 78:2226–2230

Neubert FX, Mars RB, Buch ER, Olivier E, Rushworth MF (2010) Cortical and subcortical interactions during action reprogramming and their related white matter pathways. Proc Natl Acad Sci U S A 107:13240–13245

Olivier E, Davare M, Andres M, Fadiga L (2007) Precision grasping in humans: from motor control to cognition. Curr Opin Neurobiol 17:644–648

O'Shea J, Johansen-Berg H, Trief D, Göbel S, Rushworth MF (2007a) Functionally specific reorganization in human premotor cortex. Neuron 54:479–490

O'Shea J, Sebastian C, Boorman ED, Johansen-Berg H, Rushworth MF (2007b) Functional specificity of human premotor-motor cortical interactions during action selection. Eur J Neurosci 26:2085–2095

Prado J, Clavagnier S, Otzenberger H, Scheiber C, Kennedy H, Perenin MT (2005) Two cortical systems for reaching in central and peripheral vision. Neuron 48:849–858

Prabhu G, Shimazu H, Cerri G, Brochier T, Spinks RL, Maier MA, Lemon RN (2009) Modulation of primary motor cortex outputs from ventral premotor cortex during visually guided grasp in the macaque monkey. J Physiol 587:1057–1069

Rizzolatti G, Luppino G (2001) The cortical motor system. Neuron 31:89–901

Rizzolatti G, Fabbri-Destro M, Cattaneo L (2009) Mirror neurons and their clinical relevance. Nat Clin Pract Neurol 5:24–34

Rozzi S, Calzavara R, Belmalih A, Borra E, Gregoriou GG, Matelli M, Luppino G (2006) Cortical connections of the inferior parietal cortical convexity of the macaque monkey. Cereb Cortex 16:1389–1417

Rushworth MF, Johansen-Berg H, Gobel SM, Devlin JT (2003) The left parietal and premotor cortices: motor attention and selection. Neuroimage 20:S89–S100

Sakata H, Taira M, Murata A, Mine S (1995) Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. Cereb Cortex 5:429–438

Schluter ND, Rushworth MF, Passingham RE, Mills KR (1998) Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. Brain 121:785–799

Schluter ND, Krams M, Rushworth MF, Passingham RE (2001) Cerebral dominance for action in the human brain: the selection of actions. Neuropsychologia 39:105–113

Shimazu H, Maier MA, Cerri G, Kirkwood PA, Lemon R (2004) Macaque ventral premotor cortex exerts powerful facilitation of motor cortex outputs to upper limb motoneurons. J Neurosci 24:1200–1211

Strafella AP, Paus T, Fraraccio M, Dagher A (2003) Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 126:2609–2615

Wahl M, Lauterbach-Soon B, Hattingen E, Jung P, Singer O, Volz S, Klein JC, Steinmetz H, Ziemann U (2007) Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. J Neurosci 27:2132–2138

Chapter 9
The Functional Role of Interhemispheric Interactions in Human Motor Control

Monica A. Perez

Abstract Interhemispheric interactions in the motor system have been extensively examined using transcranial magnetic stimulation (TMS). Paired-pulse TMS and the ipsilateral silent period (iSP) are the most widely used techniques to quantify interhemispheric inhibitory interactions between primary motor cortices in humans. This review will discuss the use of these techniques during unimanual and bimanual actions. The available evidence provides a framework for understanding the contribution of inhibitory interactions to the control of a resting limb during unilateral actions, while their role in the control of a limb executing a motor action remains poorly understood. Evidence shows that during bilateral actions voluntary activity of one hand can influence interhemispheric inhibitory interactions controlling the contralateral active hand. All studies point to the view that the modulation of interhemispheric interactions in the motor system changes in a task-dependent manner. These results might be of interest for patients with motor disorders and emphasizes the need of a careful interpretation when extrapolating results between different motor actions.

9.1 Introduction

During the last 20 years important insights have been gained into interhemispheric interactions in the motor system in human subjects. Since the first extensive article published by Ferbert et al. (1992), which demonstrated the feasibility of testing

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interhemispheric inhibitory processes between primary motor cortices by using transcranial magnetic stimulation (TMS), a large number of studies have been designed to study transcallosal output at rest and during motor behaviors. More recently, studies used not only double but also triple pulses to learn about interactions between both motor cortices and other more focal neuronal circuits within each primary motor cortex (Reis et al. 2008).

This chapter will review the original evidence that led to the development of paired-pulse TMS and the ipsilateral silent period (iSP) techniques used to examine interhemispheric inhibitory interactions between primary motor cortices in human subjects. Indirect and direct available evidence that support the transcallosal origin of the outcome variables examined by these techniques will be described. Important insights can be gained from analysis of the original papers that led to some of the most popular techniques used in human electrophysiology. Evidence of changes in interhemispheric inhibitory interaction between motor cortices during unilateral motor actions will be addressed. Specifically, modulation of interhemispheric inhibitory processes targeting a resting limb during different types of voluntary actions performed by the contralateral limb will be discussed. Furthermore, studies examining interhemispheric inhibitory interaction during different bilateral motor behaviors will be reviewed. The overall aim of this chapter is to discuss which aspects of motor behavior can be influenced by interhemispheric inhibitory interactions between primary motor cortices in human subjects.

9.2 Quantification of Interhemispheric Interactions in Humans

Ferbert et al. (1992), following pioneering studies by Cracco et al. (1989), published the first extensive study that revealed powerful interhemispheric interactions between primary motor cortices in intact humans by using TMS. Interhemispheric inhibition (IHI) was tested by using two magnetic stimulators to investigate the effect of a suprathreshold conditioning stimulus over one motor cortex on the size of a test motor evoked potential (MEP, test MEP) elicited by suprathreshold stimulation of the opposite motor cortex. The inhibition of the test MEP was observed at conditioning-test intervals between 6 and 15 ms and even at longer intervals when the conditioning stimulus intensity was increased. It was proposed that the inhibitory effect on the test MEP occurred at the level of the cerebral cortex. This suggestion was based on two main observations. First, in contrast to the inhibition of the test MEP evoked by TMS, test MEPs evoked by electrical stimulation were not inhibited by the contralateral magnetic conditioning stimulus. Second, the size of H-reflexes in a relaxed upper limb muscle was unaffected by the conditioning stimuli applied over the ipsilateral motor cortex. The view that this inhibitory interhemispheric effect was mediated through transcallosal pathways

was supported by later studies in patients with ischemic lesions affecting the transcallosal pathway in whom IHI was absent (Boroojerdi et al. 1996).

Transcallosal projections are a major candidate for mediating interactions between primary motor cortices at rest and during a motor behavior (Ferbert et al. 1992; Meyer et al. 1995; Franz et al. 1996). Callosal projections between arm-related motor cortical representations exist (Pandya and Vignolo 1971; Pappas and Strick 1981; Rouiller et al. 1994a, b). However, previous studies showed an uneven distribution of callosal connections between motor cortices. While these projections are more pronounced in the cortex representing movements of proximal compared to distal body parts (Gould et al. 1986; Rouiller et al. 1994a, 1994b), some of the representations of the distal limbs including the digits have dense callosal connections and some have sparse callosal projections (Gould et al. 1986), which might contribute to functional specialization of upper limb movements. It is important to consider that the density of callosal connections varies among different monkey species (Killackey et al. 1983) and may be more abundant in humans (Meyer et al. 1998). This difference may then reflect different functional levels of specialization of hand motor function between humans and monkeys. Despite the potential role of callosal pathways in mediating IHI measured by the paired-pulse TMS protocol, the evidence supporting their cortical origin of this technique remained indirect and a matter of controversy until the end of the twentieth century.

The direct evidence of the cortical origin of inhibition induced by the paired-pulse technique was provided by Di Lazzaro et al. (1999), by recording descending volleys with epidural electrodes in awake humans. In this study, corticospinal volleys evoked by TMS and electrical stimulation over the primary motor cortex were recorded from the high cervical spinal cord in three individuals with no abnormality of the motor system. It is known that a suprathreshold TMS stimulus results in multiple descending waves as recorded from epidural electrodes positioned over the spinal cord (Amassian et al. 1989). A short latency direct wave (D-wave) is followed by several longer latency indirect waves (I-waves). The D-wave is thought to result from direct depolarization of the initial axon segment of corticospinal tract neurons and is most effectively activated in human subjects by high intensity TMS or by transcranial electrical stimulation. I-waves, which follow the D-wave occur sequentially with a periodicity of approximately 1.5 ms and reflect the delay required for synaptic discharge. The reason for the periodicity is not completely understood at this time. It was proposed that it may depend on reverberating activity of circuits within the cortex or, alternatively, on changes in the membrane properties of corticospinal neurons which cause it to fire repeatedly after the application of a synchronous depolarizing stimulus. The first I-wave (I1) is thought to be generated through the depolarization of an axon synapsing directly onto a corticospinal neuron (i.e. monosynaptically), and the following I-waves (I2 and later) may require local polysynaptic circuits. Di Lazzaro et al. (1999) demonstrated that the conditioning stimulus used during testing of IHI had the largest inhibitory effect on the later (I3) descending volleys evoked by the test MEP. The I2-wave was less affected, and no inhibition was observed on the I1 volley. The authors suggested that the preferred suppression of later I-waves was

similar to the suppression observed in the intracortical inhibitory protocol (Di Lazzaro et al. 1998) tested by Kujirai et al. (1993). A main difference between these protocols is that in the intracortical protocol a subthreshold conditioning stimulus suppressed the later I-waves evoked by the test MEP at interstimulus intervals between 1 and 5 ms. This may imply that different cortical neurons are involved in the generation of the early and late I-waves and that these can be targeted differentially by conditioning procedures. It was proposed that the first and later I-waves could be generated by inputs to different parts of the pyramidal cell body. While the I1-waves may be produced by input to the basal dendrites, the later I-waves may be produced by input to the apical dendrites. Another possibility is that the later I-waves could originate from the activation of the pyramidal neurons through a pathway separate from that involved in producing the I1-wave. At present, it remains unknown whether transcallosal inhibition and intracortical inhibition use the same set of inhibitory interneurons to suppress the latest I-3 wave.

Transcallosal inhibitory function can be also estimated in humans by quantifying the iSP (Ferbert et al. 1992). Here, a single suprathreshold TMS pulse is able to inhibit ongoing voluntary EMG activity when applied to the motor cortex ipsilateral to the contracting arm. This inhibition lasts for around 30 ms and begins 10–15 ms after the minimum corticospinal conduction time to the muscle tested. The cortical origin of this inhibition was suggested by Wassermann et al. (1991) by demonstrating that H-reflexes elicited during the iSP were unchanged by the suprathreshold conditioning pulse applied over the ipsilateral primary motor cortex. Furthermore, the iSP is preserved in patients with subcortical cerebrovascular lesions that interrupted the corticospinal tract but spared the corpus callosum (Boroojerdi et al. 1996) and it is absent in patients with agenesis of the corpus callosum (Meyer et al. 1995), supporting the view that this phenomenon is mediated via the corpus callosum.

Although the two techniques, such as IHI and iSP, reflect interhemispheric inhibitory interactions between primary motor cortices, there are some differences in the time course of the inhibitory process. For example, by increasing the intensity of the conditioning pulse the magnitude of the paired-pulse TMS inhibition increased while the duration of the silent period remained stable. Interhemispheric inhibitory effects are much more variable and difficult to elicit in proximal arm muscles (i.e., biceps) compared to more distal hand muscles (i.e., flexor digitorum interosseous) when testing the iSP relative to the paired-pulse TMS protocol (Ferbert et al. 1992). Though in general there is a consensus that these two inhibitory phenomena involve transcallosal glutamatergic pathways linked with pyramidal tract neurons through GABAergic interneurons (Reis et al. 2008), the exact mechanisms mediating each of these two phenomena remain unknown.

9.3 Interhemispheric Interactions During Unilateral Motor Actions

A number of studies have proposed that interhemispheric interactions between primary motor cortices play an important role in the control of unilateral motor actions (for reviews see Carson 2005; Cincotta and Ziemann 2008). Studies that have used the paired-pulse TMS technique or the iSP to quantify transcallosal output during a unilateral motor action will be discussed in this section. It is important to note that most studies have measured transcallosal inhibitory function in the resting limb, while the contralateral limb is performing a voluntary contraction. Thus, a question that will be addressed in this section is: What aspects of unilateral motor actions may be influenced by interhemispheric inhibitory interactions between primary motor cortices in humans?

The excitability of the corticospinal pathway targeting resting upper limb muscles is influenced by the characteristics of the contralateral voluntary contraction. For instance, the sizes of MEPs tested in resting arm muscles are increased by increasing levels of tonic isometric voluntary contractions of muscles in the contralateral arm (Hess et al. 1986; Stedman et al. 1998; Tinazzi and Zanette 1998; Muellbacher et al. 2000; Hortobagyi et al. 2003; Perez and Cohen 2008, 2009a). This pronounced crossed facilitatory effect has been demonstrated in homologous (Perez and Cohen 2008, 2009a) and non-homologous (Hortobagyi et al. 2003) upper limb muscles. Whereas low levels of isometric forces have led to conflicting results including facilitation, inhibition, or no changes in MEP size tested in a resting limb (Hess et al. 1986; Stedman et al. 1998; Muellbacher et al. 2000). It is important to consider that during strong unilateral voluntary contractions muscle activity may not be restricted to the contracting arm and has also been reported in the contralateral resting arm; this is referred to as mirror electromyographic (EMG) activity (Mayston et al. 1999). The pronounced crossed facilitatory effect, reflected by an increase in the size of MEPs evoked by stimulating the primary motor cortex ipsilateral to the contracting arm, has been reported in the presence (Zijdewind et al. 2006) and also in the absence of mirror EMG activity in the resting arm (Muellbacher et al. 2000; Hortobagyi et al. 2003; Perez and Cohen 2008, 2009a). It is intriguing that similar changes are observed in corticospinal excitability in the primary motor cortex that remains at rest considering that both motor tasks are rather different. While in one task the instructions to subjects are to avoid contracting the resting limb, and therefore to intend to suppress unwanted voluntary activity in the resting arm, in the other task feedback is only provided for the strong voluntary contraction and mirror EMG activity is observed. This may imply that contraction of a muscle might provide extra excitation to the contralateral stimulated motor cortex which is subthreshold for the production of extra ongoing EMG activity, or that the increased corticospinal output is in part related to the extra muscle activity generated by the involuntary mirror EMG.

Previous evidence has demonstrated that the pronounced crossed facilitation of corticospinal drive involves changes in transmission at the cortical and spinal cord level (Meyer et al. 1995; Muellbacher et al. 2000; Perez and Cohen 2008). It has been proposed that one of the mechanisms contributing to the increase in corticospinal excitability in the resting limb is changed in interhemispheric inhibitory interactions between primary motor cortices. A study in healthy control subjects demonstrated that the magnitude of IHI targeting the resting flexor carpis radialis muscle decreases proportionally during contralateral 30 and 70 % of maximal voluntary contraction (MVC) with the same muscle representation (Perez and Cohen 2008). Figure 9.1 illustrates an example in a representative healthy control tested in the study and the group data. Note that with matched conditioned and test MEP across force levels, IHI measured in the resting flexor carpis radialis muscle was decreased at 30 % compared to 10 % of MVC and also at 70 % compared to 10 % of MVC. Importantly, the authors also reported that when the sizes of MEPs elicited by the conditioning stimulus were not adjusted to be matched across conditions, the amount of IHI targeting a resting flexor carpis radialis muscle was increased. This is in agreement with other studies that have demonstrated that the magnitude of IHI is increased in a resting limb during contralateral isometric voluntary contraction when measurements are not adjusted (Ferbert et al. 1992; Vercauteren et al. 2008; Talelli et al. 2008; Hinder et al. 2010). On one hand, it is important to note that, by adjusting the size of the conditioned MEP (MEP elicited by the conditioning stimulus), IHI is normalized to the increase in corticospinal excitability caused by the voluntary contraction. On the other hand, IHI measurements without adjusting the intensity of the conditioning stimulus which will elicit a larger MEP size in the contracting limb may be interpreted as a 'true' reflection of how IHI behaves during this motor context.

A more recent study expanded previous observations and reported that IHI measured in the resting abductor pollicis brevis muscle increased not only during increasing levels of contralateral tonic voluntary contractions but also during contralateral ballistic voluntary contractions consisting of 5–30 % of MVC (Hinder et al. 2010). In this study, it was reported that IHI modulation in the resting abductor pollicis brevis muscle was most pronounced at the higher levels of force production in contralateral homologous muscle, in both ballistic and tonic contractions. This is in agreement with the results by Perez and Cohen (2008) showing that without adjustments IHI increased proportionally to the levels of contralateral force. Together, all these studies have shown activity-dependent changes in IHI during performance of a force generation task by the opposite hand.

An intriguing question is what can be the role of these activity-dependent changes in IHI in a resting limb during these different isometric conditions? Previous studies have proposed that increments in IHI may contribute to suppress mirror EMG activity or involuntary activation of the non-active limb (Danek et al. 1992; Leinsinger et al. 1997; Mayston et al. 1999). A recent study examined systematically the hypothesis that IHI between the primary motor cortices contributes to determine the extent to which mirror EMG activity occurs in healthy controls (Hübers et al. 2008). The authors demonstrated in a first experiment that

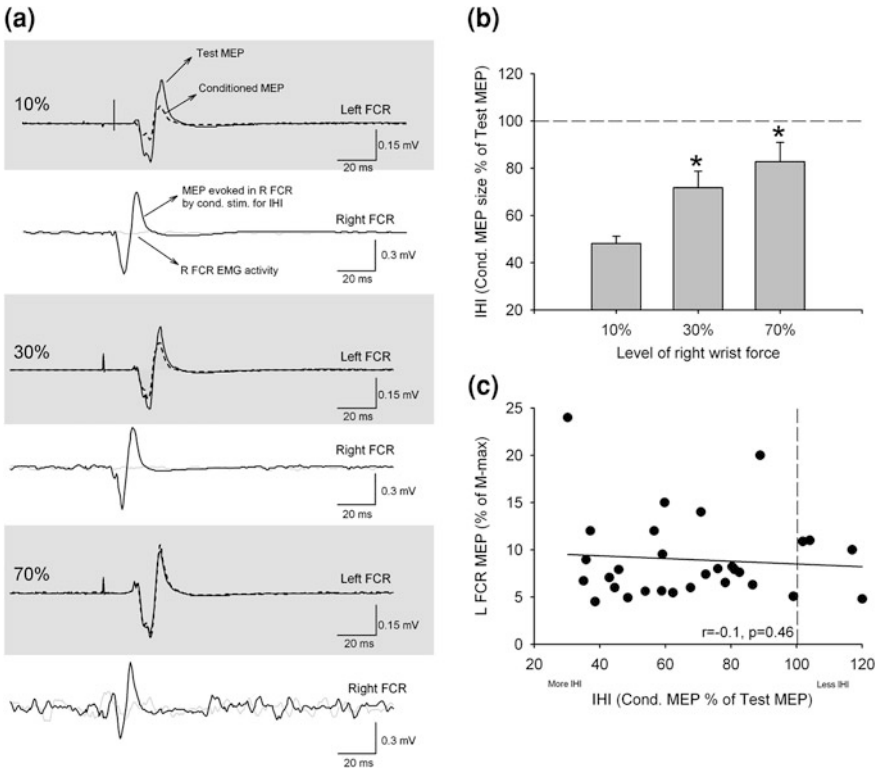

Fig. 9.1 Interhemispheric inhibition (IHI) from left to right primary motor cortex during a unilateral isometric contraction. **a** IHI from left to right primary motor cortex recorded from the left flexor carpis radialis (FCR) of a representative subject during performance of different levels of isometric right wrist flexion force (10, 30 and 70 %, *gray squares*). Test MEPs are shown in *solid lines* and conditioned MEPs in *dotted lines*. Recordings from right FCR are shown to demonstrate with *solid lines* the MEP evoked by the conditioning stimulus (for eliciting IHI) and in *light gray solid lines* the raw EMG activity in right FCR at the time of application of the test stimulus alone. Note the well defined IHI at 10 % and the progressive disinhibition shown at 30 and 70 % of maximal right wrist flexion force. **b** Group data ($n = 10$). The abscissa shows the three levels of right wrist flexion force tested (10, 30 and 70 %). The ordinate indicates the magnitude of IHI, in which the size of the conditioned MEP is expressed as a percentage of the size of test MEP amplitude. Note the progressive attenuation in IHI at 30 and 70 % of maximal right wrist flexion force (*bars* approaching the *horizontal dotted line*). **c** Relationship between IHI and left FCR maximum MEP size expressed as a percentage of the maximal motor response (M-max) at all three levels of maximal right wrist flexion force. Note that there is no relationship between MEP size and IHI. *Error bars* indicate SEs; $*p < 0.05$ [Modified from Perez and Cohen (2008)]

the magnitude of IHI and mirror EMG activity was inversely correlated. This indicated that those individuals with less mirror EMG activity in the resting limb during contralateral maximal voluntary force were those people who showed stronger IHI values measured in the non-active limb. In a second experiment, using

repetitive TMS (rTMS) over the primary motor cortex controlling the strong voluntary contraction to increase IHI, this inverse correlation between both measurements was confirmed. Importantly, in the same study, when rTMS was applied over the motor cortex controlling the mirror EMG activity, the linkage between mirror EMG activity and IHI was not present. These findings support the view that transcallosally mediated IHI from the voluntary active motor cortex to the contralateral motor cortex controlling the mirror EMG activity plays a functionally relevant role in suppressing unwanted mirror EMG activity during planned unimanual movements in intact humans.

Studies examining changes in interhemispheric interactions between primary motor cortices during phasic voluntary movements have also quantified IHI in the resting limb, while the contralateral limb is performing different isotonic actions. Previous evidence has shown that the magnitude of IHI in a resting finger muscle is increased during a metronome-paced phasic voluntary finger movement (Kobayashi et al. 2003). This is consistent with a previous study showing that self-paced finger movements suppress the size of MEPs elicited in distal and proximal arm muscles tested in the resting limb at intervals of 35–70 ms after EMG onset (Sohn et al. 2003). Similarly, it has been shown that phasic pinch (Liepert et al. 2001) and reaction time (Leocani et al. 2000) movements involving low force significantly reduce MEP amplitudes of contralateral homologous muscles, suggesting the contribution of a transcallosal mechanism for the inhibitory effect observed in these studies. Duque et al. (2005) demonstrated that corticospinal excitability of the resting first dorsal interosseous muscle was decreased to a different extent depending on the direction of the opposite index finger movement, regardless of muscles engaged in the task. It was suggested that inhibitory interactions preceding bilateral finger movements were determined by movement kinematics possibly to counteract the default production of mirror motions.

In general, when considering the changes in interhemispheric inhibitory measures between primary motor cortices during isometric and isotonic unilateral actions, it is most consistently reported that IHI is increased in both types of unilateral actions. The most common interpretation is that the magnitude of IHI contributes to control contralateral mirror EMG activity in the resting limb. Although this interpretation of the results appears to be valid, there are some considerations that also need to be taken into account when discussing the role of IHI in unilateral motor actions. IHI measured in a resting limb has been reported to be increased during a range of isometric voluntary contractions ranging from values as low as 5 % of MVC to maximal force. Mirror EMG activity in a resting limb is most commonly reported during 20 % of MVC and stronger forces (Zijdewind and Kernell 2001; Shinohara et al. 2003; Sehm et al. 2010). If a possible role of IHI is to suppress mirror EMG activity, what could be the role of this mechanism at very low levels of unilateral force, when mirror EMG activity is not found? Thus, it is important to consider that corticospinal inhibition on the side not to be moved may imply that suppression of movement is an active process and that this may be at least one of the sources for increments in the strength of interhemispheric inhibitory interactions between motor cortices at this low level of

force generation. Another consideration in this interpretation is that all the studies which actually measured IHI in a resting limb during a contralateral voluntary contraction reported no mirror EMG activity in the resting limb (Ferbert et al. 1992; Perez and Cohen 2008; Talelli et al. 2008; Vercauteren et al. 2008; Hinder et al. 2010). Furthermore, the study that measured the relationship between IHI and mirror EMG activity quantified IHI in a resting condition (Hübers et al. 2008), thus it might be argued that the evidence is not as direct as the authors proposed.

In summary, the available data provide a framework for exploring the contribution of interhemispheric inhibitory interactions between primary motor cortices in human subjects that focus on their contribution to the control of a resting limb during a contralateral unilateral voluntary action. Whereas understanding the role of interhemispheric interactions in the control of the active limb, which is basically executing the unilateral motor action, still remain poorly understood.

9.4 Interhemispheric Interactions During Bilateral Motor Actions

Most bilateral motor tasks involve simultaneous activation of a diverse number of muscle groups (for review see Scott 2000). While distal hand muscles are more occupied in performance of fine movements, proximal arm muscles play an important role in posture and stabilization (Hasan 2005; Gurfinkel et al. 2006). This combination of mobility and stability in everyday motor activities relies to a large extent on precise and coordinated muscle activation patterns. Bilateral interactions between upper limb segments have been extensively examined at the behavioral level (Kelso 1984; Carson et al. 2000; Swinnen 2002; Dounskaia et al. 2010). This section will discuss changes in physiological interactions between arm muscles during bilateral isometric and isotonic voluntary actions.

Transcallosal connections are a major candidates for mediating interactions between different arm muscles during bilateral voluntary contractions (Franz et al. 1996; Cardoso de Oliveira et al. 2001; Diedrichsen et al. 2003; Rokni et al. 2003; Ridderikhoff et al. 2005). Despite the importance of callosal pathways in interhemispheric communication, their functional role during bimanual actions remains unknown (Cardoso de Oliveira et al. 2001; Diedrichsen et al. 2003; Ridderikhoff et al. 2005). There are a few studies that describe the activity of identified motor callosal neurons in behaving animals. Studies in rabbits and cats have demonstrated low spontaneous firing rates (generally <1 spike/s) (Swadlow 1994) and little modulation in activity during locomotion or a postural stabilization task (Beloozerova et al. 2003a, b). Soteropoulos and Baker (2007) for the first time demonstrated that identified callosal neurons in a behaving primate show a low baseline firing rate of around 3.9 spike/s during a bimanual motor task. The low baseline rate of callosal neurons in awake monkeys leads to the suggestion that these cells might signal the discrete time of a motor event to the opposite

hemisphere (Soteropoulos and Baker 2007). In agreement, patients with callosal lesions show normal coupling of the hands during a discrete tapping task (Kennerley et al. 2002) and when opening a drawer with one hand and retrieving an object inside with the other (Serrien et al. 2001). However, when both hands draw circles continually, callosal patients show impairments in intermanual coupling that are similar to control subjects (Kennerley et al. 2002; Serrien et al. 2001).

Similarly, the functional role of IHI measured by the paired-pulse TMS technique remains poorly understood. Electrophysiological studies in humans conducted at rest have suggested that interhemispheric inhibitory effects between different motor cortical body representations interact closely. Ni et al. (2009) examined IHI between motor cortices by positioning one of the TMS coils (conditioning stimulus) over the hand, face, or more proximal arm representations of one motor cortex and examined their effects on responses evoked from the contralateral hand representation. It was reported that IHI was evoked from these different stimulating points, suggesting that these cortical regions might all have projections to the contralateral hand motor cortex. In agreement, a recent study tested IHI during unilateral and bilateral isometric voluntary contractions of an intrinsic distal hand muscle and a contralateral elbow flexor or extensor muscle (Soteropoulos and Perez 2011). This study demonstrated that an isometric voluntary contraction with either a distal or a proximal arm muscle, but not a foot dorsiflexor, decreases corticospinal output in a contralateral active finger muscle. IHI effects were strong during bilateral activation of distal hand muscles and weak during simultaneous activation of a distal and a proximal arm muscle, suggesting that in intact humans, crossed interactions at the level of the primary motor cortex involved different physiological mechanisms when bilateral distal hand muscles are active and when a distal and a proximal arm muscle are simultaneously active. Differences have been reported between IHI measurements taken at an inter-stimulus interval of 10 and 40 ms (Chen et al. 2003; Kukaswadia et al. 2005; Lee et al. 2007; Ni et al. 2009), including that IHI measured at an interval of 40 ms is mediated by postsynaptic gamma-aminobutyric acid type B ($GABA_B$) receptors. The transmitter system mediating IHI measured at an interval of 10 ms remains inconclusive (Irlbacher et al. 2007). In the study by Soteropoulos and Perez (2011), IHI measured at an inter-stimulus interval of 10 and 40 ms was stronger during simultaneous isometric activation of bilateral distal hand muscles. However, at the same inter-stimulus intervals, IHI was decreased during simultaneous isometric activation of a distal hand muscle and a proximal arm muscle (Fig. 9.2). This may suggest that a possible functional role for IHI measured at these different inter-stimulus intervals is to converge different information to a finger muscle from a contralateral active distal or proximal arm muscle (Fig. 9.3).

Evidence has supported the view that during generation of bimanual isometric forces transcallosal inhibition is modulated by the direction of the force (Yedimenko and Perez 2010). For example, in this study, the magnitude of IHI measured during a unilateral isometric index finger abduction task was increased during contralateral isometric index finger abduction. This increment was even

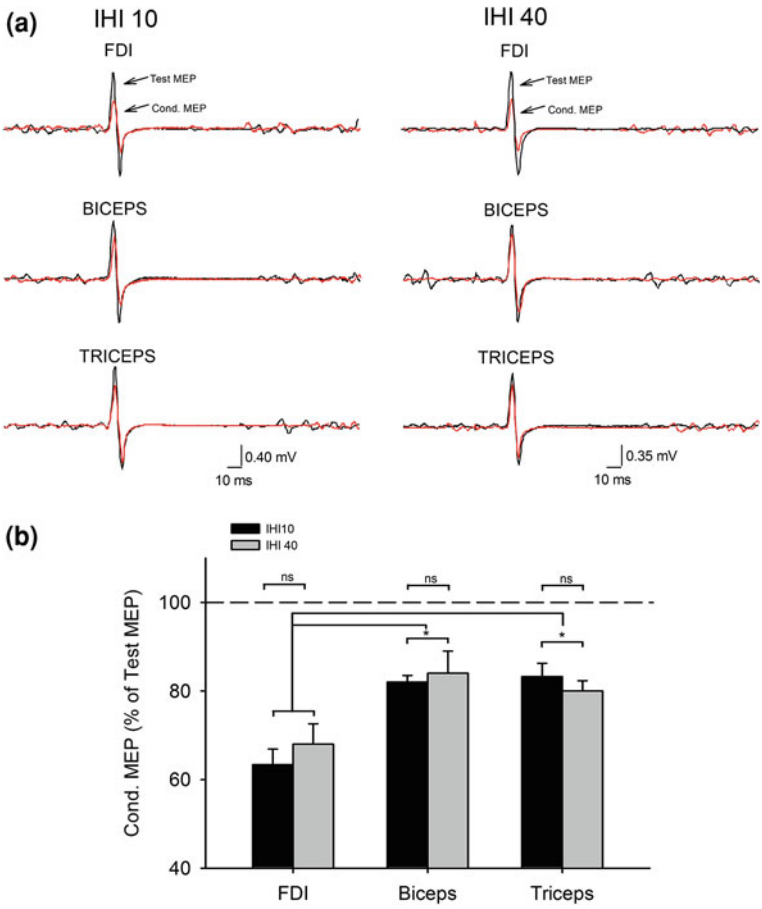

Fig. 9.2 IHI from left to right primary motor cortex during bilateral isometric contractions. **a** IHI measured at a conditioning-test interval of 10 (IHI10) and 40 ms (IHI40) recorded from the left first dorsal interosseous (FDI) of a representative subject during 10 % of left index finger abduction while the right side performed 30 % of index finger abduction or elbow flexion or extension. The specific muscle activated in the right arm is indicated as FDI, BICEPS, and TRICEPS. Test MEP and conditioned MEP (Cond. MEP) are indicated by the *arrows*. **b** Group data ($n = 9$). Abscissa shows the muscle activated in the right arm during testing of IHI10 (*black bars*) and IHI40 (*gray bars*). Ordinate indicates the magnitude of the conditioned MEP expressed as a percentage of the Test MEP. *Horizontal dashed line* represents the size of the Test MEP. Note that IHI10 and IHI40 were decreased during activation of the right biceps and triceps brachii compared with trials in which the right FDI was active. Also note there are no differences in the magnitude IHI10 and IHI40 during activation of any of the right arm muscles tested. *Error bars* indicate SEs. $*p < 0.05$ [Modified from Soteropoulos and Perez (2011)]

more pronounced when the contralateral hand performed isometric index finger adduction, irrespective of the hand posture. Therefore, during generation of index finger isometric force away from the body midline (adduction direction),

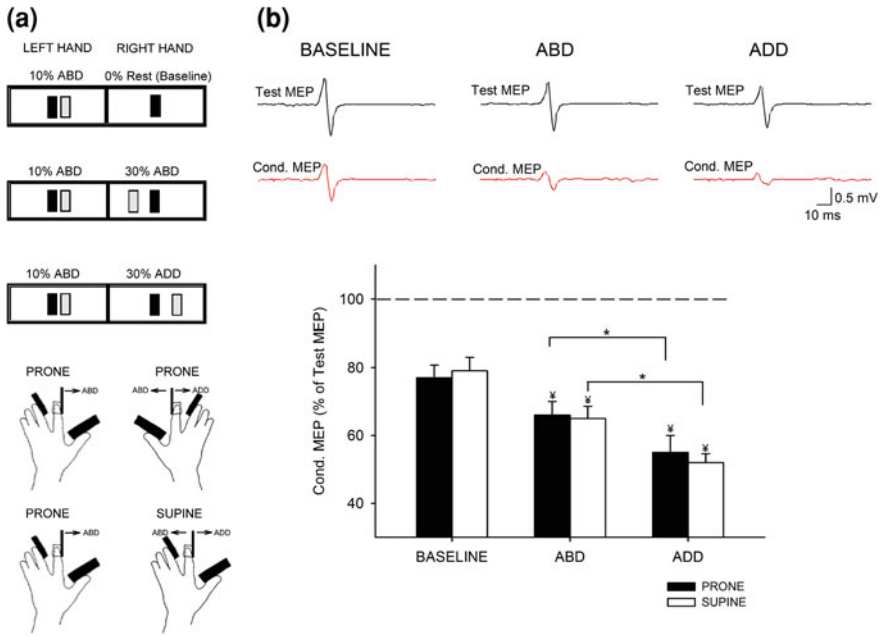

Fig. 9.3 IHI from left to right primary motor cortex during bilateral isometric contractions in different directions. **a** *Upper panel* diagram showing the visual display presented to all subjects during testing of unilateral and bilateral isometric index finger forces. Subjects were instructed on a monitor to perform 10 % of left maximal isometric index finger abduction (10 % ABD) while the right index finger remained at rest (0 % Rest) or performed 30 % of maximal isometric index finger abduction (30 % ABD) or adduction (30 % ADD) while IHI was tested in the left index finger. The condition in which the right hand remained at rest was used as baseline. The *black vertical bar* is the cursor that subjects were instructed to move by performing left and right isometric forces. The 'GO' signal (*grey box* located to the *left* or to the *right* of the cursor) was the target to where subjects had to move the cursor. The distance between cursor and target is related to the magnitude of force required to accomplish each task, normalized to the maximal voluntary effort determined in each participant. *Lower panel* schematic of the experimental set-up showing the posture of both hands during testing. The left hand was always positioned in prone posture (*palm down*) while the right hand was positioned in prone or supine (*palm up*) posture. Then, when the right index finger performed ABD in the prone position the FDI muscle was acting as an agonist to the task, whereas when the right index finger performed ABD in the *supine* position the FDI muscle was acting as an antagonist to the task. **b** *Upper panel* IHI recorded from the left FDI of a representative subject during the motor task described above. Test MEP and conditioned MEP (Cond. MEP) are indicated in all conditions tested. *Lower panel* group data ($n = 12$). The abscissa shows the conditions tested during the assessment of IHI contractions in prone (*black bars*) and supine (*white bars*) posture. The ordinate indicates the magnitude of the conditioned MEP expressed as a percentage of the Test MEP (Conditioned MEP $\times$ 100)/Test MEP) during bilateral isometric forces. The *horizontal dashed line* represents the size of the Test MEP. Note that IHI was increased to a larger extent during ADD forces regardless of the right hand posture. *Error bars* indicate SEs. $*p < 0.05$. Also note that IHI was significantly increased with respect to the baseline in all conditions tested (ø indicates significant difference with respect to baseline) [Modified from Yedimenko and Perez (2010)]

regardless of the muscle engaged in the task, IHI in the contralateral active hand was increased to a greater extent than during forces exerted toward the body midline (abduction direction), suggesting that interhemispheric interactions between primary motor cortices are driven by 'extrinsic' parameters related to the hand action. In agreement, it has been also demonstrated that coupling of bilateral isometric forces is greatly attenuated in patients with lesions of the corpus callosum, suggesting that force coupling takes place at this level (Diedrichsen et al. 2003). This is also in agreement with a recent study demonstrating that an increase in the magnitude of the iSP during bilateral compared to unilateral index finger voluntary contractions might contribute to suppress unwanted muscle activity (Giovannelli et al. 2009). Further evidence has shown that the iSP in the triceps and biceps brachii was comparable during unilateral and bilateral contraction of homologous muscles. However, during bilateral contractions of antagonist muscles (Extension–Flexion and Flexion–Extension muscle activation), less inhibition in the EMG was observed compared to bilateral contraction of homologous muscles (Perez et al. 2009).

The next question is what physiological changes occur during bilateral isotonic voluntary contractions. At present no studies have examined IHI or iSP measurements during isotonic bilateral movements in humans. However, changes in corticospinal excitability have been reported in the preparatory phase of bilateral finger movements and in the movement phase of bilateral elbow flexion and extension movements. Duque et al. (2005) demonstrated that corticospinal excitability of the resting FDI was increased during bilateral isotonic finger movements. Park and Perez 2010 showed that MEPs in the biceps and triceps brachii were increased in size while tested during bilateral elbow flexion and extension compared to a unilateral isolated movement. Several studies have shown that bimanual coordination is more stable in motor tasks requiring mirror symmetrical rather than nonsymmetrical contraction of homologous muscles (for reviews see Swinnen 2002; Swinnen and Wenderoth 2004). It is tempting to speculate that the facilitatory effect and the decreased inhibition observed in previous studies during asymmetric bilateral muscle contractions might contribute to decouple arm movements or, on the contrary, it might reflect a neural correlate of our inability to completely decouple our arms. However, previous evidence has shown that interactions between actively moving arms and those obtained when both arms are engaged in isometric contractions differ (Carson 1995). Thus, caution must be taken in extrapolation of the present results to a more dynamic task.

In summary, all these findings during bilateral isometric voluntary contractions open the possibility of accessing the hand motor cortical representation by activating a contralateral arm-related cortical region. This is in agreement with the view that the neural control of the hand can be influenced by activity originating at proximal joints (Kalaska et al. 1997). This might be of interest for patients with injuries affecting the central nervous system. The recovery of control of finger movement is one of the main problems after a lesion of the corticospinal tract in humans and nonhuman primates (Perez and Cohen 2009b). A change in the magnitude of inhibitory interhemispheric effects might help to coordinate the arms

during actions that require some degree of bimanual coupling (Rokni et al. 2003). Whereas understanding the role of interhemispheric interactions between primary motor cortices in the control of bilateral isotonic voluntary contractions still remains poorly understood.

References

Amassian VE, Cracco RQ, Maccabee PJ (1989) Focal stimulation of human cerebral cortex with the magnetic coil: a comparison with electrical stimulation. Electroencephalogr Clin Neurophysiol 74:401–416

Beloozerova IN, Sirota MG, Swadlow HA (2003a) Activity of different classes of neurons of the motor cortex during locomotion. J Neurosci 23:1087–1097

Beloozerova IN, Sirota MG, Swadlow HA, Orlovsky GN, Popova LB, Deliagina TG (2003b) Activity of different classes of neurons of the motor cortex during postural corrections. J Neurosci 23:7844–7853

Boroojerdi B, Diefenbach K, Ferbert A (1996) Transcallosal inhibition in cortical and subcortical cerebral vascular lesions. J Neurol Sci 144:160–170

Carson RG (1995) The dynamics of isometric bimanual coordination. Exp Brain Res 105:465–476

Carson RG (2005) Neural pathways mediating bilateral interactions between the upper limbs. Brain Res Brain Res Rev 49:641–662

Carson RG, Riek S, Smethurst CJ, Párraga JF, Byblow WD (2000) Neuromuscular-skeletal constraints upon the dynamics of unimanual and bimanual coordination. Exp Brain Res 131:196–214

Chen R, Yung D, Li JY (2003) Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. J Neurophysiol 89:1256–1264

Cincotta M, Ziemann U (2008) Neurophysiology of unimanual motor control and mirror movements. Clin Neurophysiol 119:744–762

Cracco RQ, Amassian VE, Maccabee PJ, Cracco JB (1989) Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. Electroencephalogr Clin Neurophysiol 74:417–424

Danek A, Heye B, Schroedter R (1992) Cortically evoked motor responses in patients with Xp22.3-linked Kallmann's syndrome and in female gene carriers. Ann Neurol 31:299–304

De Cardoso OS, Gribova A, Donchin O, Bergman H, Vaadia E (2001) Neural interactions between motor cortical hemispheres during bimanual and unimanual arm movements. Eur J Neurosci 14:1881–1896

Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, Mazzone P, Tonali P, Rothwell JC (1998) Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. Exp Brain Res 119:265–268

Di Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P, Rothwell JC (1999) Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. Exp Brain Res 124:520–524

Diedrichsen J, Hazeltine E, Nurss WK, Ivry RB (2003) The role of the corpus callosum in the coupling of bimanual isometric force pulses. J Neurophysiol 90:2409–2418

Dounskaia N, Nogueira KG, Swinnen SP, Drummond E (2010) Limitations on coupling of bimanual movements caused by arm dominance: when the muscle homology principle fails. J Neurophysiol 103:2027–2038

Duque J, Mazzocchio R, Dambrosia J, Murase N, Olivier E, Cohen LG (2005) Kinematically specific interhemispheric inhibition operating in the process of generation of a voluntary movement. Cereb Cortex 15:588–593

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. J Physiol 453:525–546

Franz EA, Eliassen JC, Ivry RB, Gazzaniga MS (1996) Dissociation of spatial and temporal coupling in the bimanual movements of callosotomy patients. Psychol Sci 7:306–310

Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Viggiano MP, Cincotta M, Ziemann U (2009) Modulation of interhemispheric inhibition by volitional motor activity: an ipsilateral silent period study. J Physiol 587:5393–5410

Gould HJ 3rd, Cusick CG, Pons TP, Kaas JH (1986) The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. J Comp Neurol 247:297–325

Gurfinkel V, Cacciatore TW, Cordo P, Horak F, Nutt J, Skoss R (2006) Postural muscle tone in the body axis of healthy humans. J Neurophysiol 96: 2678–2687

Hasan Z (2005) The human motor control system's response to mechanical perturbation: should it, can it, and does it ensure stability? J Mot Behav 37:484–493

Hess CW, Mills KR, Murray NM (1986) Magnetic stimulation of the human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. Neurosci Lett 71:235–240

Hinder MR, Schmidt MW, Garry MI, Summers JJ (2010) Unilateral contractions modulate interhemispheric inhibition most strongly and most adaptively in the homologous muscle of the contralateral limb. Exp Brain Res 205:423–433

Hortobagyi T, Taylor JL, Petersen NT, Russell G, Gandevia SC (2003) Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. J Neurophysiol 90:2451–2459

Hübers A, Orekhov Y, Ziemann U (2008) Interhemispheric motor inhibition: its role in controlling electromyographic mirror activity. Eur J Neurosci 28:364–371

Irlbacher K, Brocke J, Mechow JV, Brandt SA (2007) Effects of GABA(A) and GABA(B) agonists on interhemispheric inhibition in man. Clin Neurophysiol 118:308–316

Kalaska JF, Scott SH, Cisek P, Sergio LE (1997) Cortical control of reaching movements. Curr Opin Neurobiol 7:849–859

Kelso JA (1984) Phase transitions and critical behavior in human bimanual coordination. Am J Physiol 246:1000–1004

Kennerley SW, Diedrichsen J, Hazeltine E, Semjen A, Ivry RB (2002) Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. Nat Neurosci 5:376–381

Killackey HP, Gould HJ 3rd, Cusick CG, Pons TP, Kaas JH (1983) The relation of corpus callosum connections to architectonic fields and body surface maps in sensorimotor cortex of new and old world monkeys. J Comp Neurol 219:384–419

Kobayashi M, Hutchinson S, Schlaug G, Pascual-Leone A (2003) Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. Neuroimage 20:2259–2270

Kukaswadia S, Wagle-Shukla A, Morgante F, Gunraj C, Chen R (2005) Interactions between long latency afferent inhibition and interhemispheric inhibitions in the human motor cortex. J Physiol 563:915–924

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P,Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471: 501–519

Lee H, Gunraj C, Chen R (2007) The effects of inhibitory and facilitatory intracortical circuits on interhemispheric inhibition in the human motor cortex. J Physiol 580:1021–1032

Leinsinger GL, Heiss DT, Jassoy AG, Pfluger T, Hahn K, Danek A (1997) Persistent mirror movements: functional MR imaging of the hand motor cortex. Radiology 203:545–552

Leocani L, Cohen LG, Wassermann EM, Ikoma K, Hallett M (2000) Human corticospinal excitability evaluated with transcranial magnetic stimulation during different reaction time paradigms. Brain 123:1161–1173

Liepert J, Dettmers C, Terborg C, Weiller C (2001) Inhibition of ipsilateral motor cortex during phasic generation of low force. Clin Neurophysiol 112:114–121
Mayston MJ, Harrison LM, Stephens JA (1999) A neurophysiological study of mirror movements in adults and children. Ann Neurol 45:583–594
Meyer BU, Roricht S, von Grafin EH, Kruggel F, Weindl A (1995) Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. Brain 118:429–440
Meyer BU, Roricht S, Woiciechowsky C (1998) Topography of fibers in the human corpus callosum mediating interhemispheric inhibition between the motor cortices. Ann Neurol 43:360–369
Muellbacher W, Facchini S, Boroojerdi B, Hallett M (2000) Changes in motor cortex excitability during ipsilateral hand muscle activation in humans. Clin Neurophysiol 111:344–349
Ni Z, Gunraj C, Nelson AJ, Yeh IJ, Castillo G, Hoque T, Chen R (2009) Two phases of interhemispheric inhibition between motor related cortical areas and the primary motor cortex in human. Cereb Cortex 19:1654–1665
Pandya DN, Vignolo LA (1971) Intra- and interhemispheric projections of the precentral, premotor and arcuate areas in the rhesus monkey. Brain Res 26:217–233
Pappas CL, Strick PL (1981) Anatomical demonstration of multiple representation in the forelimb region of the cat motor cortex. J Comp Neurol 200:491–500
Park WH, Perez MA (2010) Corticospinal contribution to bilateral in-phase and out-phase arm movements. Abstract SFN, Poster 592.12/GGG17
Perez MA, Cohen LG (2008) Mechanisms underlying functional changes in the primary motor cortex ipsilateral to an active hand. J Neuroscience 28:5631–5640
Perez MA, Cohen LG (2009a) Scaling of motor cortical excitability during unimanual force generation. Cortex 45:1065–1071
Perez MA, Cohen LG (2009b) The corticospinal system and transcranial magnetic stimulation in stroke. Topics Stroke 16:254–269
Perez MA, Butler JE, Taylor JL. Transcallosal inhibition between proximal arm muscles during isometric voluntary contractions. Abstract SFN, Poster 663.2/DD3 2009
Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love ML, Perez MA, Ragert P, Rothwell JC, Cohen LG (2008) Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol 586:325–351
Ridderikhoff A, Peper CL, Beek PJ (2005) Unraveling interlimb interactions underlying bimanual coordination. J Neurophysiol 94:3112–3125
Rokni U, Steinberg O, Vaadia E, Sompolinsky H (2003) Cortical representation of bimanual movements. J Neurosci 23:11577–11586
Rouiller EM, Babalian A, Kazennikov O, Moret V, Yu XH, Wiesendanger M (1994a) Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. Exp Brain Res 102:227–243
Rouiller EM, Babalian A, Kazennikov O, Moret V, Yu XH, Wiesendanger M (1994b) Transcallosal connections of the distal forelimb representations of the primary and supplementary motor cortical areas in macaque monkeys. Exp Brain Res 102:227–243
Scott SH (2000) Role of motor cortex in coordinating multi-joint movements: is it time for a new paradigm? Can J Physiol Pharmacol 78:923–933
Sehm B, Perez MA, Xu B, Hidler J, Cohen LG (2010) Functional neuroanatomy of mirroring during a unimanual force generation task. Cereb Cortex 20:34–45
Serrien DJ, Nirkko AC, Wiesendanger M (2001) Role of the corpus callosum in bimanual coordination: a comparison of patients with congenital and acquired callosal damage. Eur J Neurosci 14:1897–1905
Shinohara M, Keenan KG, Enoka RM (2003) Contralateral activity in a homologous hand muscle during voluntary contractions is greater in old adults. J Appl Physiol 94:966–974
Sohn YH, Jung HY, Kaelin-Lang A, Hallett M (2003) Excitability of the ipsilateral motor cortex during phasic voluntary hand movement. Exp Brain Res 148:176–185

Soteropoulos DS, Baker SN (2007) Different contributions of the corpus callosum and cerebellum to motor coordination in monkey. J Neurophysiol 98:2962–2973

Soteropoulos DS, Perez MA (2011) Physiological changes underlying bilateral isometric arm voluntary contractions in healthy humans. J Neurophysiol 105:1594–1602

Stedman A, Davey NJ, Ellaway PH (1998) Facilitation of human first dorsal interosseous muscle responses to transcranial magnetic stimulation during voluntary contraction of the contralateral homonymous muscle. Muscle Nerve 21:1033–1039

Swadlow HA (1994) Efferent neurons and suspected interneurons in motor cortex of the awake rabbit: axonal properties, sensory receptive fields, and subthreshold synaptic inputs. J Neurophysiol 71:437–453

Swinnen SP (2002) Intermanual coordination: from behavioural principles to neural-network interactions. Nat Rev Neurosci 3:348–359

Swinnen SP, Wenderoth N (2004) Two hands, one brain: cognitive neuroscience of bimanual skill. Trends Cogn Sci 8:18–25

Talelli P, Waddingham W, Ewas A, Rothwell JC, Ward NS (2008) The effect of age on task-related modulation of interhemispheric balance. Exp Brain Res 186:59–66

Tinazzi M, Zanette G (1998) Modulation of ipsilateral motor cortex in man during unimanual finger movements of different complexities. Neurosci Lett 244:121–124

Vercauteren K, Pleysier T, Van Belle L, Swinnen SP, Wenderoth N (2008) Unimanual muscle activation increases interhemispheric inhibition from the active to the resting hemisphere. Neurosci Lett 445:209–213

Wassermann EM, Fuhr P, Cohen LG, Hallett M (1991) Effects of transcranial magnetic stimulation on ipsilateral muscles. Neurology 41:1795–1799

Yedimenko JA, Perez MA (2010) The effect of bilateral isometric forces in different directions on motor cortical function in humans. J Neurophysiol 104:2922–2931

Zijdewind I, Kernell D (2001) Bilateral interactions during contractions of intrinsic hand muscles. J Neurophysiol 85:1907–1913

Zijdewind I, Butler JE, Gandevia SC, Taylor JL (2006) The origin of activity in the biceps brachii muscle during voluntary contractions of the contralateral elbow flexor muscles. Exp Brain Res 175:526–535

Chapter 10
Functional Modulation of Primary Motor Cortex During Action Selection

Sven Bestmann

Abstract Primary motor cortex plays an important role in the planning and execution of movement, and motor cortical functions depend on cortical excitability. Here, we review how one can use transcranial magnetic stimulation (TMS) to study the functional changes occurring in M1 during the preparation and selection of actions. Specifically, we emphasise the idea that the brain is organised in a hierarchical way in which the boundaries between perception, cognition and action are weak and these processes occur in parallel. This, in turn, predicts that the motor system should be dynamically influenced by information about forthcoming actions we want to perform; this information is flexible and dynamic, and should be conveyed to the motor system through different routes, depending on the current context in which our actions occur. Using TMS, one can read out dynamic changes in M1 excitability in an effector-specific way, and study how such changes relate to the information that guides our actions. In humans, this provides unique insight into the physiological underpinnings and mechanism of action through which we prepare and select our movements in an ever-changing and uncertain world.

Thinking is easy, acting is difficult, and to put one's thoughts into action is the most difficult thing in the world. Johann Wolfgang von Goethe

It has now been more than 140 years since Eduard Hitzig and Gustav Fritsch performed their seminal experiments on the effect of electrical stimulation to the cerebrum (Fritsch and Hitzig 1870, 2009), yet we are still puzzled by what function the 'motor strips' identified in their experiments yield. For a long time the prevailing idea was that motor cortex and the adjacent premotor cortices are solely

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concerned with the control of muscles of the body. Little recognition had thus been given to whether the function of these regions may extend beyond connecting the brain to the lower motor neurons via the spinal cord, and to signal which particular muscles to contract. Part of this view originates from classical views of brain organisation that have emphasised that motor control is part of a serially organised system in which sensory information is transformed into neural signals for motor planning and execution through different anatomically distinct stages (Flash and Hogan 1985; Kawato et al. 1990; Bhushan and Shadmehr 1999). This transformation process ultimately culminates in M1, where descending motor commands are generated.

Perception, cognitive processing (e.g. learning, attention and working memory) and action selection have therefore traditionally been considered (and studied) as largely independent processes. The brain, however, is unlikely to adhere to these text book divisions, and while functional specialisation is critical, activity deployment in the brain does not follow these strict boundaries (Cisek 2007b; Pesaran 2010; Ledberg et al. 2007; Bullier and Nowak 1995; Hubbard et al. 2005; Smid et al. 1991; Mesulam 1990). Studies from both human and non-human primates have now, indeed, established that the premotor and motor regions of cortex, rather than being merely concerned with generating muscle commands, are intimately involved in the processing of higher order signals for action selection (Romo et al. 2004; Cisek 2007b; Cisek and Kalaska 2010; Gold and Shadlen 2001, 2007). This body of work has thus led to challenge the view of strictly serial processing as an organisational principle for brain function, and thus, our view on the foundations of action selection. For example, decisions for actions are now assumed to involve the parallel activation of multiple options, with the commitment to a specific action when activity associated to that particular action reaches a given threshold (Ivry and Spencer 2004; Cisek 2007a, b).

Studies in non-human primates, for example, show that responses of single neurons in dorsal premotor cortex (PMd) and primary motor cortex (M1) correlate with a variety of processes, such as prior expectation, time, reward, motivation or uncertainty (Bastian et al. 1998; Roesch and Olson 2003, 2004, 2007; Weinrich et al. 1984; Wise et al. 1983, 1986; Nakamura 2006; Cisek and Kalaska 2004; Crammond and Kalaska 2000, 1994; Rubino et al. 2006; Renoult et al. 2006; Requin et al. 1988; Roux et al. 2003, 2006). These signals do not directly reflect the production of the actual descending signals required for movement. At the same time, brain regions commonly regarded as specialised in, for example, decision making, learning or attention also contain neurons responding to planning and performing movements (Carello and Krauzlis 2004; Cisek and Kalaska 2005; Coe et al. 2002; Gold and Shadlen 2001; Horwitz et al. 2004; Hoshi et al. 2000; Platt and Glimcher 1999; Romo et al. 2004; Schall 2001).

The structures of the motor system are characterised by anatomical connections with a number of areas concerned with higher level computations that could provide routes through which information is transmitted to the motor system. These include regions in parietal, prefrontal and cingulate cortex, and the basal ganglia: for example, connections exist to different parietal areas (Rizzolatti et al. 1998)

involved in the representation of probabilistic information (Yang and Shadlen 2007) and reward (Platt and Glimcher 1999), but also in guiding decisions about hand choice (Oliveira et al. 2010); regions of cingulate cortex (Van Hoesen and Solodkin 1993) encoding uncertainty about reward expectation and the value of actions (Rudebeck et al. 2008); and regions of prefrontal cortex (Dum and Strick 2005; Lu et al. 1994) and subcortical basal ganglia-thalamic circuits (Alexander et al. 1990) involved in processing motivational decision variables (Schultz 2006). Within prefrontal cortex, value-based influences from ventromedial prefrontal cortex (Boorman et al. 2009) may reach the motor cortices via the anterior cingulate sulcus.

In this chapter, we address how one can usefully study the functional role and neural underpinnings of signals that might influence and bias the selection of actions in humans. How can we explain the apparent richness of signals observed in the motor system that appear to be not strictly motor related, and how these can studied in the complex and flexible behaviour only humans are capable of?

The advent of techniques for non-invasive stimulation of cortex has opened the possibility to address such issues. These techniques complement direct recordings and microstimulation approaches in animals and their impact on the functional state of M1. In this chapter, we specifically ask how one can use transcranial magnetic stimulation (TMS) to study the functional role of M1 (and PMD) for action preparation and selection, and how activity in these regions might be influenced by cognitive operations that ensure our flexible and accurate movements in an uncertain and ever-changing world. This is of relevance because it not only allows for novel insights into M1/PMd function, but also allows for inferences about the hierarchical processing for action selection.

10.1 Using Motor-Evoked Potentials to Read-Out the Functional State of M1/PMD During Behaviour

First, we briefly review how we can utilise cortical stimulation techniques such as TMS to investigate the role of the human motor system in cognition. When applied to M1, TMS can evoke descending cortico-spinal volleys that cause contralateral muscle movement. This movement can be quantified using surface electromyography and provides a direct measure of corticospinal excitability. TMS can therefore be used in humans to non-invasively assess the functional state of the corticospinal motor system (Box 10.1). The excellent temporal resolution of TMS allows for measuring the excitability of the corticospinal system at various time points within a task. Any task-specific change in the size of evoked electromyographic responses reflects changes in the functional state or excitability of the motor output system at the time of stimulation. This is a crucial asset of the technique because, in principle, changes in the functional state can now be read out with millisecond precision.

Moreover, it is often neglected that this technique provides a causal measure in its true meaning—the signal evoked in contralateral muscles is *caused* by the stimulation, and nothing else. Changes in MEP size can have different origins, including noise,

variations in wakefulness and attention, or even small variations in the precise stimulation point and can have both cortical and spinal origins. Critically, however, when carefully conducted, a significant proportion of variance will originate from changes in the functional state of the motor system at the time the TMS pulse is applied.

TMS provides a unique and complimentary measure to other techniques because, for example, the effector-specific changes in corticospinal excitability (CSE) are not easily observed otherwise, e.g. with EEG or fMRI approaches. Moreover, the possibility to assess systematic changes in intracortical inhibition and excitation (Ziemann and Rothwell 2000; Di Lazzaro et al. 1999, 2004; Kujirai et al. 1993; Chen 2004) offers unprecedented non-invasive information about their specific role in action control. Finally, as discussed in more detail elsewhere in this book, double-coil approaches (Civardi et al. 2001; Mochizuki et al. 2004) can be used together with complementary neuroimaging techniques (Bestmann et al. 2008b; Ruff et al. 2009) to highlight the functional interactions among interconnected networks in the brain, and how these may relate to the preparation and selection of action.

Box 10.1 Transcranial Magnetic Stimulation in the Motor System

In humans, TMS can be used to monitor the functional state of the corticospinal system. TMS induces an electrical current in underlying tissue, which is short lived ($\sim$200 μs) and of similar amplitude to that produced by a conventional stimulation applied directly to the surface of the brain. TMS is thought to activate the axons of neurons in the cortex and subcortical white matter underneath the stimulation coil. When applied to primary motor cortex (M1), TMS can evoke activity in peripheral muscles contralateral to the stimulation. These muscle responses, which are most readily evoked in intrinsic hand muscles, can easily be quantified using surface electromyography (EMG). The size of the evoked response is a direct measure of the excitability of the corticospinal system. As such, both cortical as well as spinal mechanisms contribute to the evoked response. This, in principle, can make it difficult to dissociate cortical from segmental influences.

However, the lowest threshold elements in M1 have inhibitory actions on motor output, likely to be mediated by GABAergic cortical interneurons. It is, therefore, possible to dissociate these cortical influences from spinal mechanisms, which are known to have higher thresholds. For example, paired-pulse protocols (Kujirai et al. 1993) make use of this by applying a low intensity conditioning pulse, and measuring its impact on the response evoked by a subsequent higher intensity test pulse.

One important point is that changes in MEP amplitude during cognitive tasks have a large contribution from such intracortical inputs. The MEP is a summation signal that reflects the series of descending volleys elicited

through cortical stimulation. An initial direct (D-) wave is evoked from the initial segment of cortico-spinal axons close to the cell body, and is followed by several successive indirect (I-) waves. Critically, the recruitment of I-waves is due to activation of the axons of excitatory interneurons. TMS can therefore activate the second-order excitatory connections possibly recruiting relatively pure later I-wave activity. Direct fast connections from PMd to the ipsilateral M1 are thought to significantly contribute to the generation of later I-waves (Groppa et al. 2011; Ziemann and Rothwell 2000). The late I-wave pathway is therefore under the control of inputs from premotor cortex. This cortico–cortical pathway has been proposed to directly influence I-wave generation in M1 cortico-spinal neurons (Sakai et al. 1997). Therefore, such pathways might play a crucial role for context-dependent changes of M1 excitability (i.e. MEP size) during action selection. Several pieces of evidence from human studies provide evidence for this idea. First, CSE in M1 during action preparation is influenced by direct inputs from PMd, as assessed with double-coil TMS experiments (Liuzzi et al. 2010), and transient interference of PMd by means of repetitive TMS leads to slowed responses (Terao et al. 2007). Moreover, there is abnormal intracortical inhibition in chronic stroke patients with spared M1, suggesting that, at least in part, inputs from other regions control this process (Hummel et al. 2009).

There are also several alternative ways to directly assess or rule out the spinal involvement in any observed MEP changes. The amplitude of the Hoffmann reflex depends upon spinal motoneuron excitability, and is evoked by stimulating the afferent fibres in peripheral nerves. The so-called F-wave is a centrifugal discharge recorded by EMG and evoked in spinal motoneurons by antidromic excitation of the motoneuron axon–soma. Comparing these responses with the responses of the TMS-evoked MEP allows for dissociating cortical from spinal effects.

10.2 Assessing the Functional State of M1 During Action Execution/Voluntary Movement

One question TMS allows for addressing is how the functional state of M1 changes during the execution phase of an action. This can be investigated by probing M1 excitability at different times immediately prior to, during and after the overt response during simple or choice RT and stop-signal tasks (Chen et al. 1998; Davey et al. 1998; Soto et al. 2010; Leocani et al. 2000; Hiraoka et al. 2010; Chen and Hallett 1999; Hasbroucq et al. 2000; Romaiguere et al. 1997). Interestingly, as discussed below, the specific changes in M1 during this period may differ from those in the preceding period of action preparation.

One consistently observed finding is that CSE increases immediately before the electromyographic burst in the agonist muscle that precedes the actual voluntary movement (Hoshiyama et al. 1996a, 1997), which often corresponds to the period

starting around 100 ms after the appearance of an imperative ('Go') stimulus. Moreover, this effect is accompanied by a reduction in intracortical inhibition preceding the voluntary movement by around 100 ms (Reynolds and Ashby 1999). It, therefore, seems that intracortical inhibition is involved in simple and choice RT tasks, even when there is no requirement to stop the movement (Burle et al. 2004). This increase is furthermore mirrored by a (usually much smaller) CSE increase (Hoshiyama et al. 1996b; Duque and Ivry 2009; Koch et al. 2006; Leocani et al. 2000), or even significant decrease (Michelet et al. 2010; Tandonnet et al. 2010; Liepert et al. 2001) in muscles not involved in an action. This latter pattern may depend on whether a muscle is merely not involved, or an antagonistic to the selected muscle. It is important to recall, however, that intracortical facilitation (ICF) and ICI as well as different dynamic behaviours of ICF and pre-movement facilitation may change simultaneously and influence one another. Depending on their relative contribution in a specific task, and the specific time at which we measure CSE, the specific pattern of CSE changes that can be observed thus may vary significantly (see above). The consistent observation is that there are very specific and mostly antagonistic changes in CSE between the selected and unselected effectors during the execution of an action. Taken together, these results show how TMS can provide unique insight into the physiological processes in M1 during the execution of selected actions.

10.3 Assessing the Functional State of M1 During Action Preparation

It is generally thought that actions are prepared and selected before they are executed. For example, we know from behavioural reaction time experiments that prior information (such as visual cues) can be used to prepare actions (Rosenbaum 1980). One hallmark feature in these experiments is a shortening of reaction times for more predictable stimuli, which has been taken as evidence that the respective action has been 'mentally' prepared, and therefore a response can be made with greater speed once the imperative stimulus is presented.

The most successful approach to study preparation experimentally are instructed delay tasks, in which a cue stimulus provides information about the likely action, which can only be executed after a delay when a subsequent imperative stimulus has been presented. This period prior to an overt action is therefore unconfounded by descending motor commands, and thus can provide useful insights into the physiological mechanism that underpin the transformation of perceptual and cognitive signals into action. The point is that under a parallel processing account, we expect to see gradual changes in CSE in the period prior to action, when actions are prepared.

In non-human primates, neurons representing the selected action progressively increase their firing rates during a delay period inserted between presentation of a visual cue and the appearance of a visual stimulus. This increase depends, for example, on the degree of predictability of the forthcoming movement—on

average, more predictable sensory information leads to a stronger gradual activity build-up in premotor and motor cortex (Roux et al. 2006; Wise et al. 1983; Tanji and Evarts 1976; Bastian et al. 1998; Cisek and Kalaska 2005; Cisek 2005; Crammond and Kalaska 2000, 1994; Nakamura 2006). This observation is seen as a physiological correlate of action preparation.

In humans, TMS has been used to assess preparatory activity changes non-invasively, using delayed-response or instructed delay tasks. A rich set of studies have now established the general finding that CSE undergoes significant changes during action preparation (Bestmann et al. 2008a; van den et al. 2007; Coxon et al. 2006; van Elswijk et al. 2007, 2008; Mars et al. 2008; Duque and Ivry 2009; Duque et al. 2010; Hasbroucq et al. 1997, 1999a, b; Sinclair and Hammond 2008, 2009; Touge et al. 1998; Mars et al. 2007). These findings demonstrate that in humans, TMS can serve as a non-invasive analogue to invasive direct recordings of delay-period activity in non-human primates. TMS allows for differentiating between different intrinsic muscles, and thus provides sufficient resolution to distinguish the physiological underpinnings of action preparation and selection for different unilateral finger movements (Bestmann et al. 2008a). Moreover, the ability to assess intracortical inhibition and facilitation non-invasively through the use of paired-pulse protocols (Kujirai et al. 1993; Di Lazzaro et al. 2004) provides an additional window into the physiological interplay between intracortical excitation and inhibition during the preparation and selection of different actions.

Box 10.2 It Is Up, It Is Down! What are the Specific Physiological Changes in M1 During Action Preparation?

A general and consistent finding is that CSE is modulated during action preparation in an effector-specific way, but it is less clear what direction such changes should have. For example, both effector-specific increases and decreases in CSE as well as increases and releases (disinhibition) from intracortical inhibition during action preparation have been reported. This is initially surprising—how can the same preparatory process lead to opposite physiological changes in the motor system? One important factor that can partly account for such discrepancies is how such increases or decreases are measured. For example, CSE measures obtained at rest are often used as a baseline for comparison with delay-period activity. This does not control for task-related factors such as arousal, attention, or vigilance. In other words, the motor system ‘at rest’ might indeed be very different in many ways other than preparation or action selection from the motor system during a task. Comparing CSE during a delay period with CSE at rest may simply tell us that rest and task are different, but often precludes more specific inferences. Comparing CSE changes between prepared versus unprepared responses during a task provides a more controlled assessment compared to merely

asking whether a change occurs relatively to a resting control period. For example, delay-period CSE may be reduced relative to some neutral resting baseline period, with effector-specific changes (e.g. a significantly larger CSE for the selected versus unselected action) on top of this overall period of relative inhibition. Moreover, the changes in preparatory activity may further depend on whether one has to select one hand over the other, or whether selection is required between different digits of the same hand. While the former requires interhemispheric processes, the latter might predominantly engage response competition processes within a hemisphere.

Cognitive models suggest that several types of behavioural inhibition take place during action preparation. Selected actions need to be prepared, but at the same time unselected and possibly conflicting actions need to be suppressed. Moreover, any type of response needs to be withheld until the appropriate time to respond is reached. At that point, prepared but withheld responses need to be released, whereas inhibition for inappropriate responses needs to be maintained. From this, it becomes immediately evident that physiological correlates of these processes can only be assessed, when one can isolate the specific type of behavioural inhibition, and that changes in CSE can easily reflect a time-dependent compound signal of several processes occurring at the same time that may, in sum, lead to an increase or decrease in CSE.

Some of the discrepancies in the literature on action preparation may thus stem from the different comparisons made across different studies. To this author, the debate whether CSE increases or decreases during action preparation seems to be slightly superfluous—the critical question is whether there is a preparation-specific and effector-specific change in CSE. Both increases and decreases (inhibition) could then be meaningful options depending on the specific context in which CSE is measured, and may reflect the different types of behavioural inhibition that are often required for successful action preparation and action execution.

10.4 Studying Dynamic, Trial-By-Trial Changes in M1 Excitability During Action Preparation

A fundamental feature of human movement is that anticipatory knowledge of an impending action improves the speed and accuracy of the response. This implies that we learn about the predictability of sensory information, and modify activity at the level of motor output accordingly, while preparing an action. For example, although sensory information provides useful cues for guiding actions, it is also inherently uncertain, and learning about this uncertainty can enable the nervous system to prepare motor output for action prior to an event. There is a good deal of information showing that, on average, predictable sensory information guiding actions leads to a gradual activity build-up in premotor and motor cortex during

preparation for action. This may also be reflected in specific excitability changes of corticospinal projections, in line with a burgeoning set of studies demonstrating quantifiable effects of visual information on the motor system, including the spinal cord. Taken together, this implies that the predictability of sensory information is learned and represented explicitly in the brain, and that its representation is directed to the level of motor output for anticipatory action preparation.

The important point here is that predictability and prior expectations can only be established through learning, and that the functional state of the motor system should, therefore, reflect such learning. This interesting dynamic, however, cannot be revealed by inspecting M1 excitability changes on average alone. Understanding how the brain uses the predictability of events to inform preparation for action requires models of how, for example, the predictability of an event is learnt and represented over time. One solution to this is the use of model-based approaches (Mars et al. 2010; Corrado and Doya 2007; O'Doherty et al. 2007). These can provide trial-by-trial predictions about the possible rules used by the motor system to harness the probability of future events for action decisions.

In a first study investigating whether predictive (in this case, information theoretic) models can explain a substantial amount of CSE changes during action preparation, we previously measured CSE during an instructed delay task, in which an instruction cue provided information about the forthcoming movement with varying degree of certainty (Bestmann et al. 2008a). Thus, participants had to respond to an imperative cue stimulus but critically, in different blocks of trials, a preceding instruction cue predicted the identity of this imperative cue only with 85, 70 or 55% validity, respectively (Fig. 10.1a). This, therefore, varied the uncertainty about the required action, given the instruction cue. The important point here is that these probabilities were unknown to the participants, and thus had to be learned over time in each block.

Behavioural data showed that participants reacted, on average, faster on trials in which the instruction cue was more reliable, indicating some sort of learning that enabled more efficient action preparation (Fig. 10.1b). But this does not reveal the dynamics through which this learning may take place, and influence action preparation. We therefore quantified the uncertainty about the forthcoming movement on a trial-by-trial basis for each block basis, using a simple information theoretic model that quantified the uncertainties inherent in trial sequences. We therefore asked whether these quantities might predict subject's responses and their preparatory state prior to these (as measured through CSE). RTs and muscle-specific CSE changes were indeed influenced by both entropy and surprise: High uncertainty (high entropy) about the upcoming imperative cue was associated with decreases in CSE during the preparatory period (Fig. 10.1c). Moreover, a surprising imperative cue on the preceding trial resulted in a similar decrease in CSE. Thus, delay-period CSE, which provides an index of the preparatory state of a subject was lower when preparatory cues resolved less uncertainty (entropy), and when surprise in the preceding trigger cues was large (Fig. 10.1c). This effect was mirrored in the behavioural reaction time data—subjects were slower to respond when average uncertainty about the forthcoming movement was high, and furthermore, when imperative stimuli were surprising given the preceding cue (Fig. 10.1c).

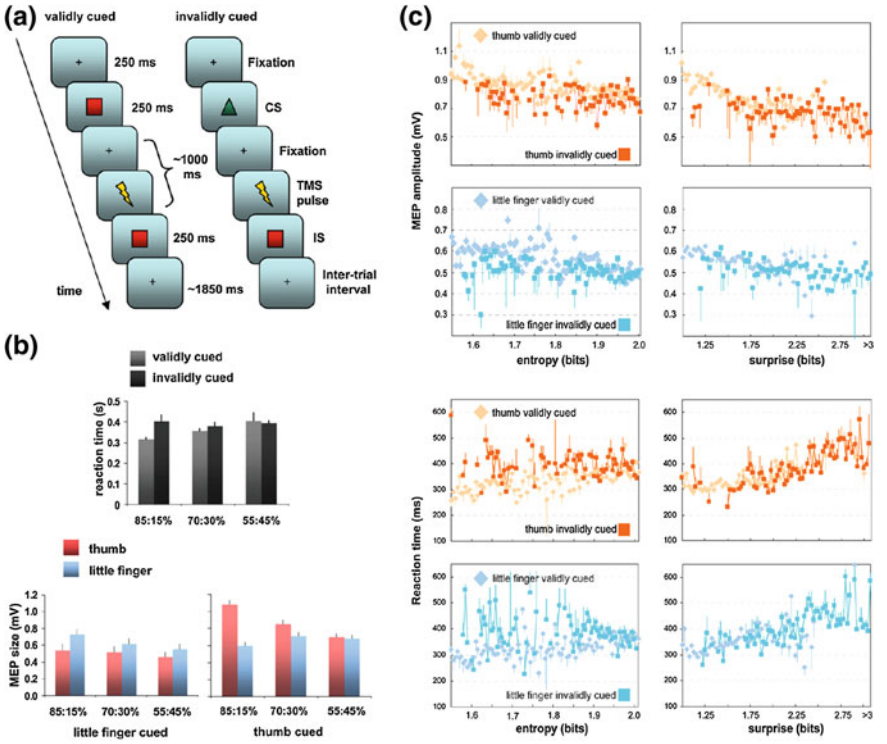

Fig. 10.1 Influence of uncertainty and surprise on corticospinal excitability during action preparation. **a** Schematic of the task. On valid trials, a preparatory CS predicted the identity of a subsequent IS, cueing a button press with the right thumb or little finger. On invalid trials, the CS-IS mapping was invalid as the CS was followed by the alternative IS. The validity of the CS varied across blocks of 105 trials between 85:15, 70:30 and 55:45%, respectively, creating blocks with, low, medium and high uncertainty about imperative stimuli. A single TMS pulse was applied during every trial, 200 ms before IS appearance, to read out changes in M1 excitability. **b** Average behavioural and electrophysiological results. Reaction times (*grey/black*) are, on average, significantly shorter for more predictable (i.e. more validly cued) actions. Average changes in corticospinal excitability parallel this effect, with CSE being largest for prepared actions in a predictable context. **c** CSE (*top*) for validly and invalidly cued trials from all subjects, plotted against the average uncertainty (entropy; *left*) and trial-by-trial surprise (*right*). CSE was generally higher when uncertainty (entropy) was low, and trials were preceded by surprising events. Reaction times for validly and invalidly cued trials plotted against average uncertainty (entropy; *left*) and trial-by-trial surprise (*right*). Reaction times were generally faster when uncertainty (entropy) and surprise were low. These results suggest that predictions about events based on both the average uncertainty, and trial-by-trial surprise conveyed by visual events can modulate the voluntary motor system on a trial-by-trial basis. Furthermore, these results show how measurements of corticospinal excitability with TMS can provide a window to examine computational processes about how humans implement decisions in real time.

One important aspect is the use of Bayesian model comparison, to test whether the specific model chosen indeed provides a good explanation of the data, compared to other competing models. This model comparison showed that there was indeed more evidence supporting the specific information theoretic model (given the observed RT and the CSE data), compared to a small group of alternative models that did not, or not fully, account for the contextual uncertainty inherent in the sequence of trials. The novel point made by these data is that human motor cortex is dynamically biased according to (inferred or learned) representations of contextual probabilities inherent in imperative visual events. These representations are likely encoded in the brain upstream of M1, but dynamically influence action preparation and selection. Recent support that this may reflect a general mechanism through which representations for actions are shaped by current contextual requirements comes from work on value-based decisions for actions (Klein-Flügge and Bestmann 2012). If action selection in motor regions emerges from a competitive process that is gradually biased by evidence signals originating in other regions, then biases reflecting the evaluation of more or less valuable choice options should be traceable in the motor system, before the decision process is complete. Using TMS to read-out CSE changes during such value-based decisions, Klein-Flügge and Bestmann (2012) found that excitability for chosen versus unchosen actions indeed distinguishes the forthcoming choice, but critically so could demonstrate that this occurs before the decision process is complete. Importantly, this required a trial-by-trial quantification of the value that participants assigned to their choices. The subjective value that participants assigned to the options offered on each trial was inferred using cumulative prospect theory (cf. Tversky and Kahnemann 1992), which could then be regressed against the dynamic trial-by-trial changes in CSE. Support for the idea that the observed dynamic changes in CSE during the choice process were indeed value-driven comes from the finding that both excitability and reaction times varied as a function of the subjective value difference between chosen and unchosen actions, and that such a relationship does not occur in the absence of a decision. This provides novel evidence in humans, using non-invasive TMS as read-out of the functional state of motor cortex, that internally generated value-based decisions influence the competition between action representations in motor cortex before the decision process is complete. More generally, these results demonstrate the importance of studying the dynamic, trial-by-trial changes that guide the preparation and selection of movements in an ever-changing world, and that such dynamics can now be usefully studied with the combination of TMS and model-based approaches.

10.5 Frameworks for Action Selection

The studies reviewed above clearly show that the human motor system is dynamically shaped by our prior expectations about forthcoming movements. Such prior expectations can be instilled by variables that are currently relevant for action

selection, such as the expected reward that can be obtained following an action, or the likelihood of an event occurring. TMS can reveal the dynamic changes in the functional state of M1 during and prior to actions, and how these relate to our prior expectations.

However, these findings themselves do not yet provide a mechanistic account that can explain the functional role of such modulations and influences, nor how such signals actually reach the motor system. It is now established that M1 exhibits responses to sensory signals in a variety of modalities including vision and somatosensation (Hatsopoulos and Suminski 2011), and thus is likely to integrate such signals for the selection and preparation of appropriate movements. Two recent theories provide architectures and mechanistic accounts on how this may actually happen—the affordance competition hypothesis (Cisek 2006, 2007a, b; Cisek and Kalaska 2010) and active inference (Friston et al. 2009, 2011b). We note that these two accounts are not competing or mutually exclusive—in fact, it is the subject of intense ongoing research to explore their commonalities. We briefly outline the core concepts of these accounts and how they help to explain the findings reviewed above, but any discussion of these accounts in the present chapter can only be brief, and the reader is referred to the original work for in-depth details.

10.5.1 Affordance Competition

The key point of the affordance competition hypothesis (Cisek and Kalaska 2010) is that sensory information is continuously used to specify potentially available, and competing actions, whilst other kinds of information (such as motivation, reward expectation, new sensory information) will be accumulated and provide evidence that ultimately leads to selecting one action from the available set of actions (Cisek 2006, 2007b; Cisek and Kalaska 2010). Potential actions therefore 'compete' with one another, and internal representations influence this competition. As initially introduced by (Gibson 1979), the concept of affordances reflects the idea that these internal representations are opportunities, or affordances, for action defined by the environment (Fig. 10.2).

These affordances for action are based on incoming sensory information and internally represented decision variables (e.g. subjective reward, motivation, wakefulness, hunger), which are continuously transformed into parameters of action (Cisek and Kalaska 2010). This also implies that multiple actions might initially be available, but competition between these alternative options ultimately leads to the commitment to one specific action. This competition is thought to be driven by mutual inhibition among cells with different tuning properties (Cisek 2006), and/or through differential selection in corticostriatal circuits as likely physiological substrates.

Critically, the competition at the level of PMd/M1 is driven by inputs from other regions, such as parietal and prefrontal cortex and the basal ganglia that

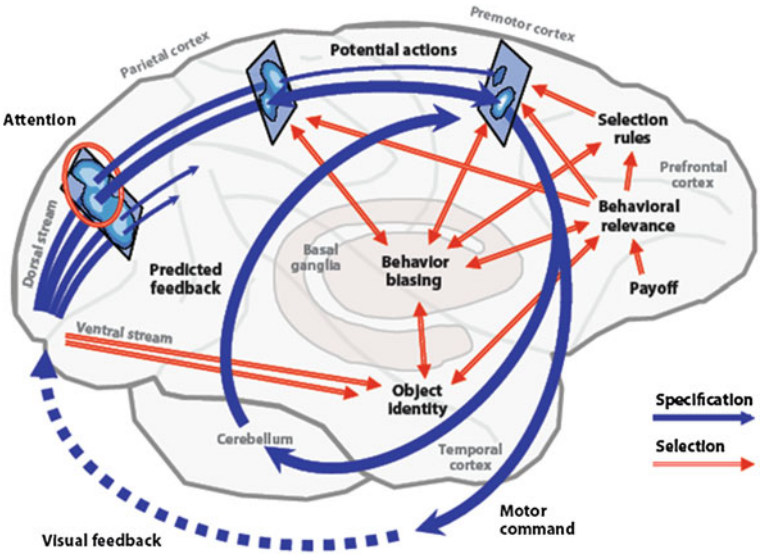

Fig. 10.2 Graphical illustration of the affordance competition hypothesis. Sensory information (here illustrated for visual information flow) continuously influences the representation of potentially available actions, which 'compete' with one another. Internal representations and signals such as motivation, reward expectation, new sensory information provide additional evidence that ultimately leads to selecting one action from the available set of actions. As shown here, starting with the visual cortex, information is passed to the parietal lobe, where visual information is likely transformed into representations of potential actions. These representations are captured by different, and potentially competing neural populations in parietal cortex. This competition is biased by additional input from e.g. the basal ganglia and prefrontal cortical regions that accumulate and process additional information required for action selection (here indicated by the *red arrows*). Once competition has led to the selection of an action over its potential action alternatives, it is unleashed. This also caused feedback from the induced changes in the environment (*dotted blue arrow*) and feedback caused by the predictive collateral via the cerebellum. Modified with permission from Cisek and Kalaska (2010)

contain information or evidence about the most appropriate action, given the context. These regions therefore bias the competition among actions until some (unspecified) threshold is reached and a commitment to an action is made.

The TMS work in humans reviewed above indeed provides strong support for this idea. The observation that CSE changes relate to the prior expectation of an event, for example, suggest that our expectation of what will happen (and consequently what we will have to do) 'biases' the competition among available actions. In humans, this bias can be quantified using TMS. For example, a recent study by Michelet and co-workers shows that CSE during the reaction time of the Eriksen flanker task increases gradually for the agonist muscle, and decreases for the antagonistic muscle (Michelet et al. 2010). Critically, the opposite is initially observed in an incongruent condition—when information about which action to perform is misleading, the competition among two actions initially favours the erroneous action, and only later reverses as sensory information provides sufficient

evidence for the correct action. This is reflected in the observed CSE changes which initially increase for the erroneous action, and then reverse gradually. These findings elegantly show that the dynamic modulation in CSE resembles the competition among alternative actions, which ultimately leads to the selection of one response and the rejection of the other.

10.5.2 Active Inference and Predictive Coding

Active inference is a corollary of the free-energy principle and the predictive coding account (Friston and Kiebel 2009). In short, this idea states that a self-organising system like the brain should minimise the free energy of sensory states it samples. Here, free energy itself is an upper bound on the surprise (prediction error) associated with sensory signals, such as visual cues. Simply put, free energy is the (Bayesian) evidence for the brain's model of its world. This means that when the brain minimises free energy, it reduces surprising exchanges with the world. Equivalently, it means that it maximises the evidence for its own internal model of its sensory world (see Fig. 10.3).

More specifically, predictive coding is based on the assumption that the brain makes inferences about the causes of its own sensations and percepts (see Feldman and Friston 2010; Friston 2006, 2009, 2010; Friston et al. 2010; Friston and Stephan 2007). These inferences are driven (or inhibited) by bottom-up or feed-forward sensory information (see Fig. 10.3). This information is conveyed to higher brain areas in the form of prediction errors (Rao and Ballard 1999; Friston et al. 2008). By contrast, top-down or backward connections signal the predictions the brain makes about the information that will be received at the lower level. These predictions aim at suppressing prediction errors. An ideal state would be when predictions are optimal, and prediction errors therefore are minimal, i.e. the brain would perfectly explain (predict) the world which it samples through its own sensations.

One important concept is that of top-down first-order and contextual second-order predictions. The former drive (or inhibit) neurons reporting prediction errors, whereas the latter reflect the precision (or reliability) of these predictions errors. Put simply, the precision can be regarded as representing the reliability, ambiguity, or uncertainty about sensory signals, such as visual cues. As seen previously, there is a rich body of work that shows that the motor system is highly sensitive to such second-order effects, e.g. changes in the reliability of visual cues instructing movement (Bestmann et al. 2008a; Brown et al. 2011; Mars et al. 2007). Top-down predictions can therefore have a direct (first-order) or a modulatory (second-order) effect on the responses of prediction error units that make the ensuing predictions as efficient as possible.

Active inference (Brown et al. 2011; Friston et al. 2011b) extends this architecture, suggesting that exactly the same recursive message passing also applies to the motor system. The only difference here is that prediction errors at the lowest

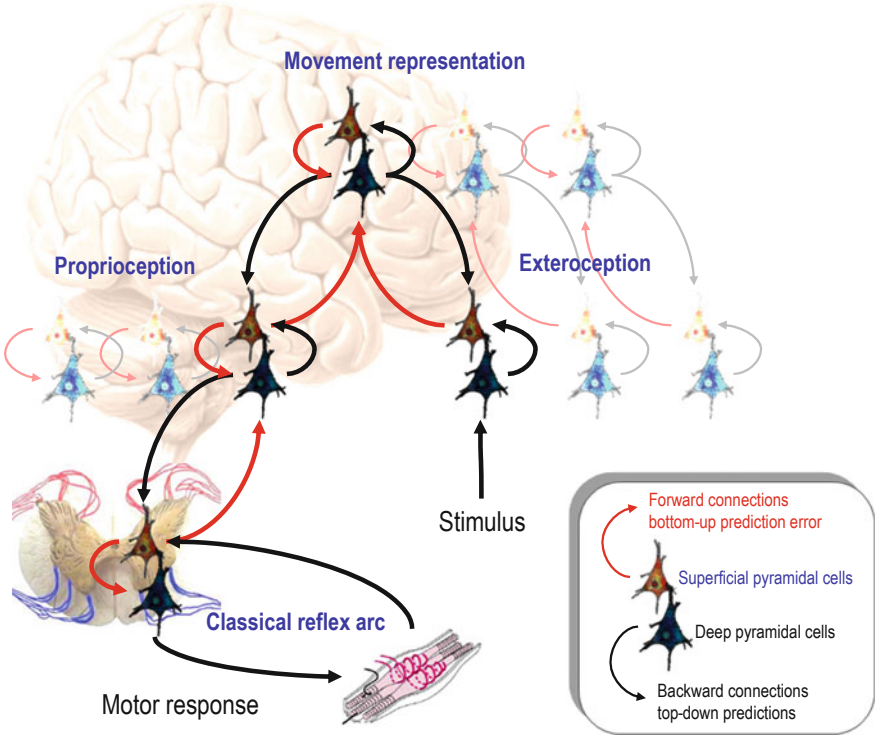

Fig. 10.3 Active inference and predictive coding. Active inference is a generalisation of predictive coding that covers motor behaviours and itself is a special instance of the principle of free energy minimisation (cf. Friston et al. 2011b). Free energy is a statistical quantity that bounds the surprise (self-information) associated with sensory signals. This surprise is quantified in relation to a generative model of how those signals were caused. Predictive coding uses prediction error as a proxy for free energy (cf. surprise) and rests on a hierarchical model, in which prediction errors are passed up the hierarchy (*red arrows*) to optimise high-level representations that provide top-down predictions (*black arrows*). In this schematic, prediction error units are portrayed in *red* and units encoding the conditional expectations of the hidden causes of sensory input are shown in *blue*. During perception, the best explanation for sensory input emerges when the top-down predictions can explain as much of the prediction error (at each hierarchical level) as possible. Active inference takes this one step further and notes that certain sensory modalities can use prediction errors to drive motoneurons to eliminate prediction error directly (through classical motor reflex arcs). This is shown schematically on the lower left, using units in the dorsal and ventral horns of the spinal cord. Under active inference, a movement just fulfils the predictions afforded by percepts that predict both exteroceptive (e.g. visual) and interoceptive (e.g. stretch receptor) consequences. This high-level (sensorimotor) percept is activated by an exteroceptive (sensory) cue, and the ensuing top-down predictions propagate to both sensory cortex (to suppress exteroceptive prediction error) and the motor system. However, in the motor system, the predictions engender a prediction error that is eliminated by movement (adapted from Brown et al. 2011)

level (i.e. the cranial nerve nuclei and spinal cord) are suppressed by movement, through classical reflex arcs. In this view, descending (corticospinal) signals are not motor commands in the traditional sense per se, but predictions of the

proprioceptive signals that arise from movement. The peripheral motor system, through movement, therefore tries to fulfil its predictions about proprioceptive signals (see Friston (2009, 2010) for an in-depth treatment). In this view, a sensory cued movement is generated by a high-level (sensorimotor) representation that predicts a particular pattern of proprioceptive and exteroceptive sensory signals. This representation arises to explain prediction errors caused by, e.g., a visual cue, while motor reflexes suppress the ensuing prediction errors in the proprioceptive domain. This framework has been used to explain several features of the motor system and a series of behaviours, from visual tracking (Friston 2009; Friston and Kiebel 2009), motor preparation (Brown et al. 2011), to action observation (Friston et al. 2010). An obvious appeal of this idea is that the same architecture and principle about hierarchical message passing and integration can now be applied to both sensory and motor systems. This has intuitive appeal because it assumes that the brain does not use different approaches for dealing with similar problems.

In other words, this framework provides a unifying account for the organizational principles underpinning sensory perception and action: if ascending sensory signals are prediction errors and descending motor commands are predictions, then the optimisation of predictions (and the resulting movements) should depend on optimising precision (i.e. reliability) in exactly the same way as in sensory processing. Initial modelling work and behavioural experiments (Brown et al. 2011) support this view. These suggest that motor preparation (and selection) is ultimately directed towards proprioceptive sensations, i.e., the predicted sensory feedback that will be elicited from the anticipated motor response (Brown et al. 2011).

Importantly, both concepts can be brought together when considering that high-level sensorimotor representations are often dynamic in nature. Time variant neural dynamics represent prior beliefs or expectations about, for example, the sequence of sensorimotor events or trajectories that will arise in the near future (Friston et al. 2011a). One way of viewing these is as attractors that provide proprioceptive and sensory predictions for sensorimotor integration. These, in other words, are the representations of affordance. The selection of an action relies on accurate bottom-up prediction errors conveying salient sensory information that has yet to be explained. Or, phrased differently, the brain aims to select those representations with an affordance that best explains sensory input, which is equivalent to affordance competition. Put simply, bottom-up prediction errors bias competition amongst high(er) level sensorimotor representations (attractors).

The key point here is that both accounts introduced here predict that our motor system will be influenced by the predictions our brain makes about forthcoming movements, and that they make specific statements on how such influences originate. For example, the affordance competition model provides testable predictions about the likely routes through which specific types of information will be conveyed to the motor system; this depends on the functional specialisation of regions in parietal or frontal cortex, and the basal ganglia. Recent double-coil TMS studies have indeed addressed how, for example, premotor and parietal regions influence the functional state of M1 during different types of movement tasks, and at rest (Koch et al. 2006, 2007, 2008). Active inference, and the hierarchical

predictive coding account it is resting on, makes specific predictions about the type of connections that convey the information that allows for an action to be chosen and executed. Bottom-up sensory information (prediction errors) that has yet to be explained by top-down predictions is generally associated with the activity of superficial pyramidal cells (Mumford 1992; Friston et al. 2010; Brown et al. 2011). With regards to action selection, descending (cortico-spinal) signals are not motor commands in the traditional sense per se, but predictions of the proprioceptive signals that arise from movement. In the future, it will therefore be of interest to record from the different descending and ascending pathways, and to determine whether information in these may indeed reflect movement-related predictions and prediction errors, respectively. Both accounts vary in their specific aims, complexity and architecture. However, they provide frameworks in which to address how information influences our motor system to ensure that our actions remain flexible and accurate in an uncertain and ever-changing world.

10.6 Summary

Transcranial magnetic stimulation (TMS) provides a window to examine *computational processes* that the brain may use to implement actions in real time, and their influence on output stage. In humans, TMS can thus be used to *read-out* the functional state of motor system during action preparation and selection, and thus provide insights into their physiological underpinnings in an unprecedented way.

Outstanding Questions

- The role of intracortical inhibition and excitation for action preparation and selection remain poorly understood. What are their roles for specifying selected versus unselected actions, and for withholding actions from premature release? Moreover, what are the specific roles of different types of intracortical inhibition? Previous work has largely focused on $GABA_A$-mediated short ICI, but paired-pulse TMS protocols allow for assessing $GABA_B$-type inhibition as well. More generally, what is the functional role of various physiological signatures that can be assessed through TMS?
- A system in which decision making, learning, attention, and action selection and preparation occur in parallel clearly does not imply that no more functional specialisation is required. But then an unresolved question is how specialiszed brain regions interact, to convey evidence about forthcoming actions. What are the physiological mechanisms through which information is integrated in an action-specific way?

- A large body of work has established how our motor cortex excitability changes during preparation of movements, and the subsequent execution of an action. Past attempts have failed, however, to find physiological markers of the point when the commitment to an action occurs. In other words, when has enough evidence for one versus another action been accumulated, so that the final action is unleashed? Can TMS, for example, be used to determine this point?

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References

Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 85:119–146

Bastian A, Riehle A, Erlhagen W, Schoner G (1998) Prior information preshapes the population representation of movement direction in motor cortex. NeuroReport 9:315–319

Bestmann S, Harrison LM, Blankenburg F, Mars RB, Haggard P, Friston KJ, Rothwell JC (2008a) Influence of uncertainty and surprise on human corticospinal excitability during preparation for action. Curr Biol 18:775–780

Bestmann S, Ruff CC, Blankenburg F, Weiskopf N, Driver J, Rothwell JC (2008b) Mapping causal interregional influences with concurrent TMS-fMRI. Exp Brain Res 191:383–402

Bhushan N, Shadmehr R (1999) Computational nature of human adaptive control during learning of reaching movements in force fields. Biol Cybern 81:39–60

Boorman ED, Behrens TE, Woolrich MW, Rushworth MF (2009) How green is the grass on the other side? frontopolar cortex and the evidence in favor of alternative courses of action. Neuron 62:733–743

Brown H, Friston K, Bestmann S (2011) Active inference, attention, and motor preparation. Front Hum Neurosci 2:A218

Bullier J, Nowak LG (1995) Parallel versus serial processing: new vistas on the distributed organization of the visual system. Curr Opin Neurobiol 5:497–503

Burle B, Vidal F, Tandonnet C, Hasbroucq T (2004) Physiological evidence for response inhibition in choice reaction time tasks. Brain Cogn 56:153–164

Carello CD, Krauzlis RJ (2004) Manipulating intent: evidence for a causal role of the superior colliculus in target selection. Neuron 43:575–583

Coe B, Tomihara K, Matsuzawa M, Hikosaka O (2002) Visual and anticipatory bias in three cortical eye fields of the monkey during an adaptive decision-making task. J Neurosci 22:5081–5090

Chen R (2004) Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp Brain Res 154:1–10

Chen R, Hallett M (1999) The time course of changes in motor cortex excitability associated with voluntary movement. Can J Neurol Sci 26:163–169

Chen R, Yaseen Z, Cohen LG, Hallett M (1998) Time course of corticospinal excitability in reaction time and self-paced movements. Ann Neurol 44:317–325

Cisek P (2005) Neural representations of motor plans, desired trajectories, and controlled objects. Cogn Process 6:15–24

Cisek P (2006) Integrated neural processes for defining potential actions and deciding between them: a computational model. J Neurosci 26:9761–9770
Cisek P (2007a) A parallel framework for interactive behavior. Prog Brain Res 165:475–492
Cisek P (2007b) Cortical mechanisms of action selection: the affordance competition hypothesis. Philos Trans R Soc Lond B Biol Sci 362:1585–1599
Cisek P, Kalaska JF (2004) Neural correlates of mental rehearsal in dorsal premotor cortex. Nature 431:993–996
Cisek P, Kalaska JF (2005) Neural correlates of reaching decisions in dorsal premotor cortex: specification of multiple direction choices and final selection of action. Neuron 45:801–814
Cisek P, Kalaska JF (2010) Neural mechanisms for interacting with a world full of action choices. Annu Rev Neurosci 33:269–298
Civardi C, Cantello R, Asselman P, Rothwell JC (2001) Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. Neuroimage 14:1444–1453
Corrado G, Doya K (2007) Understanding neural coding through the model-based analysis of decision making. J Neurosci 27:8178–8180
Coxon JP, Stinear CM, Byblow WD (2006) Intracortical inhibition during volitional inhibition of prepared action. J Neurophysiol 95:3371–3383
Crammond DJ, Kalaska JF (1994) Modulation of preparatory neuronal activity in dorsal premotor cortex due to stimulus-response compatibility. J Neurophysiol 71:1281–1284
Crammond DJ, Kalaska JF (2000) Prior information in motor and premotor cortex: activity during the delay period and effect on pre-movement activity. J Neurophysiol 84:986–1005
Davey NJ, Rawlinson SR, Maskill DW, Ellaway PH (1998) Facilitation of a hand muscle response to stimulation of the motor cortex preceding a simple reaction task. Mot Control 2:241–250
Di Lazzaro, V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P, Rothwell JC (1999) Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. Exp Brain Res 124:520–524
Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Mazzone P, Insola A, Tonali PA, Rothwell JC (2004) The physiological basis of transcranial motor cortex stimulation in conscious humans. Clin Neurophysiol 115:255–266
Dum RP, Strick PL (2005) Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. J Neurosci 25:1375–1386
Duque J, Ivry RB (2009) Role of corticospinal suppression during motor preparation. Cereb Cortex 19:2013–2024
Duque J, Lew D, Mazzocchio R, Olivier E, Ivry RB (2010) Evidence for two concurrent inhibitory mechanisms during response preparation. J Neurosci 30:3793–3802
Feldman H, Friston KJ (2010) Attention, uncertainty, and free-energy. Front Hum Neurosci 4:215
Flash T, Hogan N (1985) The coordination of arm movements: an experimentally confirmed mathematical model. J Neurosci 5:1688–1703
Friston K (2009) The free-energy principle: a rough guide to the brain? Trends Cogn Sci 13:293–301
Friston K (2008) Hierarchical models in the brain. PLoS Comput Biol 4:e1000211
Friston K (2010) The free-energy principle: a unified brain theory? Nat Rev Neurosci 11:127–138
Friston K, Kiebel S (2009) Predictive coding under the free-energy principle. Philos Trans R Soc Lond B Biol Sci 364:1211–1221
Friston KJ, Stephan KE (2007) Free-energy and the brain. Synthese 159:417–458
Friston K, Kilner J, Harrison L (2006) A free energy principle for the brain. J Physiol Paris 100:70–87
Friston KJ, Daunizeau J, Kiebel SJ (2009) Reinforcement learning or active inference? PLoS One 4:e6421
Friston KJ, Daunizeau J, Kilner J, Kiebel SJ (2010) Action and behavior: a free-energy formulation. Biol Cybern 102:227–260
Friston K, Shiner T, Fitzgerald T, Galea J, Adams R, Brown H, Dolan R, Moran R, Stephan KE, Bestmann S (2011a) Dopamine, precision and affordance in active inference. Plos Comp Biol 8:e1002327

Friston K, Mattout J, Kilner J (2011b) Action understanding and active inference. Biol Cybern 104:137–160
Fritsch G, Hitzig E (1870) Über die elektrische Erregbarkeit des Grosshirns. Arch Anat Physiol Wissen 37:300–332
Fritsch G, Hitzig E (2009) Electric excitability of the cerebrum (Uber die elektrische Erregbarkeit des Grosshirns). Epilepsy Behav 15:123–130
Gibson JJ (1979) The ecological approach to visual perception. Houghton Mifflin, Boston
Gold JI, Shadlen MN (2001) Neural computations that underlie decisions about sensory stimuli. Trends Cogn Sci 5:10–16
Gold JI, Shadlen MN (2007) The neural basis of decision making. Annu Rev Neurosci 30:535–574
Groppa S, Schlaak BH, Munchau A, Werner-Petroll N, Dunnweber J, Baumer T, van Nuenen BF, Siebner HR (2011) The human dorsal premotor cortex facilitates the excitability of ipsilateral primary motor cortex via a short latency cortico-cortical route. Hum Brain Mapp 33:419–430
Hasbroucq T, Kaneko H, Akamatsu M, Possamai CA (1997) Preparatory inhibition of cortico-spinal excitability: a transcranial magnetic stimulation study in man. Brain Res Cogn Brain Res 5:185–192
Hasbroucq T, Kaneko H, Akamatsu M, Possamai CA (1999a) The time-course of preparatory spinal and cortico-spinal inhibition: an H-reflex and transcranial magnetic stimulation study in man. Exp Brain Res 124:33–41
Hasbroucq T, Osman A, Possamai CA, Burle B, Carron S, Depy D, Latour S, Mouret I (1999b) Cortico-spinal inhibition reflects time but not event preparation: neural mechanisms of preparation dissociated by transcranial magnetic stimulation. Acta Psychol (Amst) 101:243–266
Hasbroucq T, Akamatsu M, Burle B, Bonnet M, Possamai CA (2000) Changes in spinal excitability during choice reaction time: the H reflex as a probe of information transmission. Psychophysiology 37:385–393
Hatsopoulos NG, Suminski AJ (2011) Sensing with the motor cortex. Neuron 72:477–487
Hiraoka K, Kamata N, Matsugi A, Iwata A (2010) Premovement facilitation of corticospinal excitability before simple and sequential movement. Percept Mot Skills 111:129–140
Hoshiyama M, Kitamura Y, Koyama S, Watanabe S, Shimojo M, Kakigi R (1996a) Reciprocal change of motor evoked potentials preceding voluntary movement in humans. Muscle Nerve 19:125–131
Hoshi E, Shima K, Tanji J (2000) Neuronal activity in the primate prefrontal cortex in the process of motor selection based on two behavioral rules. J. Neurophysiol 83:2355–2373
Horwitz GD, Batista AP, Newsome WT (2004) Representation of an abstract perceptual decision in macaque superior colliculus. J. Neurophysiol 91:2281–2296
Hoshiyama M, Kitamura Y, Koyama S, Watanabe S, Shimojo M, Kakigi R (1996b) Reciprocal change of motor evoked potentials preceding voluntary movement in humans. Muscle Nerve 19:125–131
Hoshiyama M, Kakigi R, Koyama S, Takeshima Y, Watanabe S, Shimojo M (1997) Temporal changes of pyramidal tract activities after decision of movement: a study using transcranial magnetic stimulation of the motor cortex in humans. Electroencephalogr Clin Neurophysiol 105:255–261
Hubbard EM, Piazza M, Pinel P, Dehaene S (2005) Interactions between number and space in parietal cortex. Nat Rev Neurosci 6:435–448
Hummel FC, Steven B, Hoppe J, Heise K, Thomalla G, Cohen LG, Gerloff C (2009) Deficient intracortical inhibition (SICI) during movement preparation after chronic stroke. Neurology 72:1766–1772
Ivry RB, Spencer RM (2004) The neural representation of time. Curr Opin Neurobiol 14:225–232
Kawato M, Maeda Y, Uno Y, Suzuki R (1990) Trajectory formation of arm movement by cascade neural network model based on minimum torque-change criterion. Biol Cybern 62:275–288
Koch G, Franca M, Del Olmo MF, Cheeran B, Milton R, Alvarez SM, Rothwell JC (2006) Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. J Neurosci 26:7452–7459

Koch G, Franca M, Mochizuki H, Marconi B, Caltagirone C, Rothwell JC (2007) Interactions between pairs of transcranial magnetic stimuli over the human left dorsal premotor cortex differ from those seen in primary motor cortex. J Physiol 578:551–562

Koch G, Fernandez DO, Cheeran B, Schippling S, Caltagirone C, Driver J, Rothwell JC (2008) Functional interplay between posterior parietal and ipsilateral motor cortex revealed by twin-coil transcranial magnetic stimulation during reach planning toward contralateral space. J Neurosci 28:5944–5953

Klein-Flügge MC, Bestmann S (2012) Time-dependent changes in human corticospinal excitability reveal value-based competition for action during decision processing. J Neurosci 32:8373–8382

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501–519

Ledberg A, Bressler SL, Ding M, Coppola R, Nakamura R (2007) Large-scale visuomotor integration in the cerebral cortex. Cereb Cortex 17:44–62

Leocani L, Cohen LG, Wassermann EM, Ikoma K, Hallett M (2000) Human corticospinal excitability evaluated with transcranial magnetic stimulation during different reaction time paradigms. Brain 123(Pt 6):1161–1173

Liepert J, Dettmers C, Terborg C, Weiller C (2001) Inhibition of ipsilateral motor cortex during phasic generation of low force. Clin Neurophysiol 112:114–121

Liuzzi G, Horniss V, Hoppe J, Heise K, Zimerman M, Gerloff C, Hummel FC (2010) Distinct temporospatial interhemispheric interactions in the human primary and premotor cortex during movement preparation. Cereb Cortex 20:1323–1331

Lu MT, Preston JB, Strick PL (1994) Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. J Comp Neurol 341:375–392

Mars RB, Bestmann S, Rothwell JC, Haggard P (2007) Effects of motor preparation and spatial attention on corticospinal excitability in a delayed-response paradigm. Exp Brain Res 182:125–129

Mars RB, Hulstijn W, Toni I (2008) Selection, preparation, and monitoring: current approaches to studying the neural control of action. Cortex 44:479–481

Mars RB, Shea NJ, Kolling N, Rushworth MF (2010) Model-based analyses: promises, pitfalls, and example applications to the study of cognitive control. Q J Exp Psychol (Colchester) 29:1–16

Mesulam MM (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 28:597–613

Michelet T, Duncan GH, Cisek P (2010) Response competition in the primary motor cortex: corticospinal excitability reflects response replacement during simple decisions. J Neurophysiol 104:119–127

Mochizuki H, Huang YZ, Rothwell JC (2004) Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. J Physiol 561:331–338

Mumford D (1992) On the computational architecture of the neocortex. II. The role of cortico-cortical loops. Biol Cybern 66:241–251

Nakamura K (2006) Neural representation of information measure in the primate premotor cortex. J Neurophysiol 96:478–485

O'Doherty JP, Hampton A, Kim H (2007) Model-based fMRI and its application to reward learning and decision making. Ann N Y Acad Sci 1104:35–53

Oliveira FT, Diedrichsen J, Verstynen T, Duque J, Ivry RB (2010) Transcranial magnetic stimulation of posterior parietal cortex affects decisions of hand choice. Proc Natl Acad Sci U S A 107:17751–17756

Pesaran B (2010) Neural correlations, decisions, and actions. Curr Opin Neurobiol 20:166–171

Platt ML, Glimcher PW (1999) Neural correlates of decision variables in parietal cortex. Nature 400:233–238

Rao RP, Ballard DH (1999) Predictive coding in the visual cortex: a functional interpretation of some extra-classical receptive-field effects. Nat Neurosci 2:79–87

Renoult L, Roux S, Riehle A (2006) Time is a rubberband: neuronal activity in monkey motor cortex in relation to time estimation. Eur J Neurosci 23:3098–3108
Requin J, Riehle A, Seal J (1988) Neuronal activity and information processing in motor control: from stages to continuous flow. Biol Psychol 26:179–198
Reynolds C, Ashby P (1999) Inhibition in the human motor cortex is reduced just before a voluntary contraction. Neurology 53:730–735
Rizzolatti G, Luppino G, Matelli M (1998) The organization of the cortical motor system: new concepts. Electroencephalogr Clin Neurophysiol 106:283–296
Roesch MR, Olson CR (2003) Impact of expected reward on neuronal activity in prefrontal cortex, frontal and supplementary eye fields and premotor cortex. J Neurophysiol 90:1766–1789
Roesch MR, Olson CR (2004) Neuronal activity related to reward value and motivation in primate frontal cortex. Science 304:307–310
Roesch MR, Olson CR (2007) Neuronal activity related to anticipated reward in frontal cortex: does it represent value or reflect motivation? Ann N Y Acad Sci 1121:431–446
Romaiguere P, Possamai CA, Hasbroucq T (1997) Motor cortex involvement during choice reaction time: a transcranial magnetic stimulation study in man. Brain Res 755:181–192
Romo R, Hernandez A, Zainos A (2004) Neuronal correlates of a perceptual decision in ventral premotor cortex. Neuron 41:165–173
Rosenbaum DA (1980) Human movement initiation: specification of arm, direction, and extent. J Exp Psychol Gen 109:444–474
Roux S, Coulmance M, Riehle A (2003) Context-related representation of timing processes in monkey motor cortex. Eur J Neurosci 18:1011–1016
Roux S, MacKay WA, Riehle A (2006) The pre-movement component of motor cortical local field potentials reflects the level of expectancy. Behav Brain Res 169:335–351
Rubino D, Robbins KA, Hatsopoulos NG (2006) Propagating waves mediate information transfer in the motor cortex. Nat Neurosci 9:1549–1557
Rudebeck PH, Bannerman DM, Rushworth MF (2008) The contribution of distinct subregions of the ventromedial frontal cortex to emotion, social behavior, and decision making. Cogn Affect Behav Neurosci 8:485–497
Ruff CC, Driver J, Bestmann S (2009) Combining TMS and fMRI: from 'virtual lesions' to functional-network accounts of cognition. Cortex 45:1043–1049
Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I (1997) Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. Exp Brain Res 113:24–32
Schall JD (2001) Neural basis of deciding, choosing and acting. Nat Rev Neurosci 2:33–42
Schultz W (2006) Behavioral theories and the neurophysiology of reward. Annu Rev Psychol 57:87–115
Sinclair C, Hammond GR (2008) Reduced intracortical inhibition during the foreperiod of a warned reaction time task. Exp Brain Res 186:385–392
Sinclair C, Hammond GR (2009) Excitatory and inhibitory processes in primary motor cortex during the foreperiod of a warned reaction time task are unrelated to response expectancy. Exp Brain Res 194:103–113
Smid HG, Lamain W, Hogeboom MM, Mulder G, Mulder LJ (1991) Psychophysiological evidence for continuous information transmission between visual search and response processes. J Exp Psychol Hum Percept Perform 17:696–714
Soto O, Valls-Sole J, Kumru H (2010) Paired-pulse transcranial magnetic stimulation during preparation for simple and choice reaction time tasks. J Neurophysiol 104:1392–1400
Tandonnet C, Garry MI, Summers JJ (2010) Cortical activation during temporal preparation assessed by transcranial magnetic stimulation. Biol Psychol 85:481–486
Tanji J, Evarts EV (1976) Anticipatory activity of motor cortex neurons in relation to direction of an intended movement. J Neurophysiol 39:1062–1068
Terao Y, Furubayashi T, Okabe S, Mochizuki H, Arai N, Kobayashi S, Ugawa Y (2007) Modifying the cortical processing for motor preparation by repetitive transcranial magnetic stimulation. J Cogn Neurosci 19:1556–1573

Touge T, Taylor JL, Rothwell JC (1998) Reduced excitability of the cortico-spinal system during the warning period of a reaction time task. Electroencephalogr Clin Neurophysiol 109:489–495
Tversky A , Kahneman D (1992) Advances in prospect theory: cumulative representation of uncertainty. J Risk Uncertainty 5:297–323
van den HP, Mars RB, van Elswijk G, Hegeman J, Pasman JW, Bloem BR, Toni I (2007) Online maintenance of sensory and motor representations: effects on corticospinal excitability. J Neurophysiol 97:1642–1648
van Elswijk G, Kleine BU, Overeem S, Stegeman DF (2007) Expectancy induces dynamic modulation of corticospinal excitability. J Cogn Neurosci 19:121–131
van Elswijk G, Schot WD, Stegeman DF, Overeem S (2008) Changes in corticospinal excitability and the direction of evoked movements during motor preparation: a TMS study. BMC Neurosci 9:51
Van Hoesen GW, Solodkin A (1993) Some modular features of temporal cortex in humans as revealed by pathological changes in Alzheimer's disease. Cereb Cortex 3:465–475
Weinrich M, Wise SP, Mauritz KH (1984) A neurophysiological study of the premotor cortex in the rhesus monkey. Brain 107(Pt 2):385–414
Wise SP, Weinrich M, Mauritz KH (1983) Motor aspects of cue-related neuronal activity in premotor cortex of the rhesus monkey. Brain Res 260:301–305
Wise SP, Weinrich M, Mauritz KH (1986) Movement-related activity in the premotor cortex of rhesus macaques. Prog Brain Res 64:117–131
Yang T, Shadlen MN (2007) Probabilistic reasoning by neurons. Nature 447:1075–1080
Ziemann U, Rothwell JC (2000) I-waves in motor cortex. J Clin Neurophysiol 17:397–405

Chapter 11
Enhancement of Normal Cognitive Abilities Through Noninvasive Brain Stimulation

Alvaro Pascual-Leone, Jared C. Horvath and Edwin M. Robertson

Abstract The last several decades has seen a dramatic influx in the desire for and research exploring neuroenhancement (the betterment of human cognition and/or behavior via the direct manipulation of neural processes at the chemical and cellular level). Although this movement has largely been predominated by pharmaceutical intercession, recent literature concerning noninvasive electromagnetic (EM) stimulation suggests these devices may contain strong neuroenhancement capabilities. In this chapter, we review the EM literature with the aim of addressing the following questions: 1) what might the mechanisms of EM neuroenhancement be?, 2) what specific behaviors or cognitive abilities does research suggest may be amenable to EM neuroenhancement?, and 3) what might EM neuroenhancement reveal about basic human brain function? Following this review, we conclude that, although certainly exciting, the field of EM neuroenhancement too young to engender any definitive proclamations regarding efficacy. In addition, we make a series of suggestions regarding research protocols which may aid in the future elucidation of EM neuroenhancement mechanisms and effects.

11.1 Introduction

A desire for personal enhancement appears to be a defining trait of human beings. Whether via education, training, or the development of unique tools and technologies, man has long attempted to overcome the physical and mental limitations

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of the human body. Take, for instance, the hammer: a device that increases the force human beings can exert on a given target. Or the bicycle: a device that increases the speed with which human beings can travel and work. These and other tools allow people to achieve feats beyond natural ability and, accordingly, can be defined as early enhancement technologies.

In our own times, the concept of human enhancement has shifted from external aides and naturalistic manipulation to nascent scientific, body/brain-based intervention. Genetic engineering, pharmaceutical development, synthetic biocultivation: tools originally designed for remediation are, today, being increasingly utilized for transcendence. Unlike the above devices, these new technologies aim to enhance physical performance not externally, but internally via chemical and cellular changes. Neuroenhancement—betterment of human cognition and behavior via the direct manipulation of neural processes, is an example of one such 'internal' approach, which has likely been encouraged by (1) our greater understanding on the mechanisms of action of such 'internal' manipulations, (2) the realization that human biology, more specifically the human brain, does not optimize for any one given behavior but, rather, optimizes for behavioral flexibility (Kapur 2011); and (3) the apparently insatiable social desire (and pressure) for ever increasing human abilities (Farah et al. 2004; Chatterjee 2004, 2007).

Neuroenhancement can take varied forms and approaches (for review: Farah et al. 2004). Here, we focus on the use of noninvasive electromagnetic (EM) brain stimulation. Several promising EM devices, including Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS), originally developed to aid in the characterization of human brain physiology, the understanding of brain-behavior relations, and the mapping and healing of afflicted brains (Wagner et al. 2007), are currently being utilized by people ranging from simple at-home engineers to members of the US Armed Forces aiming to enhance physical and cognitive performance (Fox 2011). Aside from the ethical issues surrounding neuroenhancement, which have been well explored in the literature (Farah et al. 2004; Chatterjee 2007; Dees 2007; Eastman 2007), other important questions remain when considering EM-mediated neuroenhancement: How might EM enhancement occur? In other words, how exactly can brain stimulation translate into better performance? What aspects of human behavioral performance or cognition may be amenable to EM enhancement? What has the research to date revealed concerning these enhancement possibilities? If such neuroenhancement is possible, what does it tell us about human brain function? What might be the cost, side effects, and undesirable consequences of such EM enhancement? In the present chapter we aim to address these questions.

11.2 Electromagnetic Enhancement: A Conceptual Framework

EM stimulation is fundamentally a mode of modulation of activity in distributed neural networks. As such, EM enhancement must be conceptualized in the context of brain network effects and EM-induced behavioral effects as related to

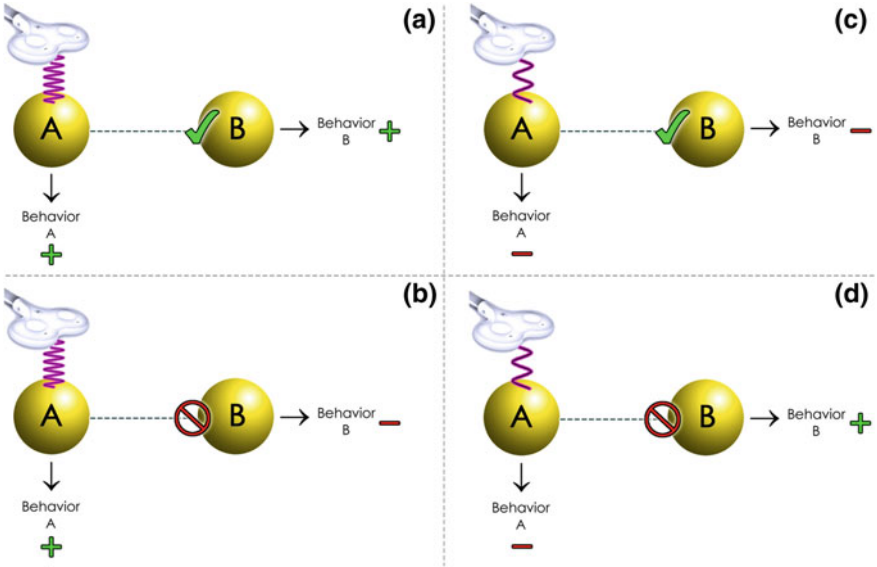

Fig. 11.1 EM stimulation can serve to transiently modulate the activity of a discrete brain region which, via trans-synaptic effects, can further impact any diffuse neural network with which the target interacts. These distributed effects can vary according to stimulation parameters and functional neural relationships. For instance, if the target node sends excitatory signals to a secondary node, then excitatory stimulation will increase these afferences effectively enhancing activity in both nodes and enhancing network activation (**a**). Conversely, if the target node sends inhibitory signals to a secondary node, then excitatory stimulation will increase these inhibitory afferences effectively suppressing activity in later node and shifting network activation in a more complex manner (**b**). If the target node sends excitatory signals to a secondary node, then inhibitory stimulation will decrease these afferences effectively inhibiting activity in both nodes (**c**). Interestingly, if the target node sends inhibitory signals to a secondary node, then inhibitory stimulation will decrease these afferences effectively enhancing activity in the later node (**d**). This form of enhanced distal activity via local inhibitory stimulation is known as *paradoxical facilitation*

modulated activity across dynamic distributed brain networks. Figures 11.1 and 11.2 schematically illustrate a few key principles. Accounting for such variable network effects of EM stimulation, one may conceive of three broad mechanisms by which EM stimulation might enhance behavioral performance: *zero-sum, stochastic resonance, and entrainment enhancement.*

11.3 Zero-Sum Enhancement

In game theory, the term 'zero-sum' refers to a situation whereby every gain is counterbalanced by an equal yet opposing loss elsewhere (Fig. 11.3). For instance, in a game of head's up poker, the money one *gains* is necessarily a *loss* for another player—although money has changed hands, there has been no overall quantitative shift.

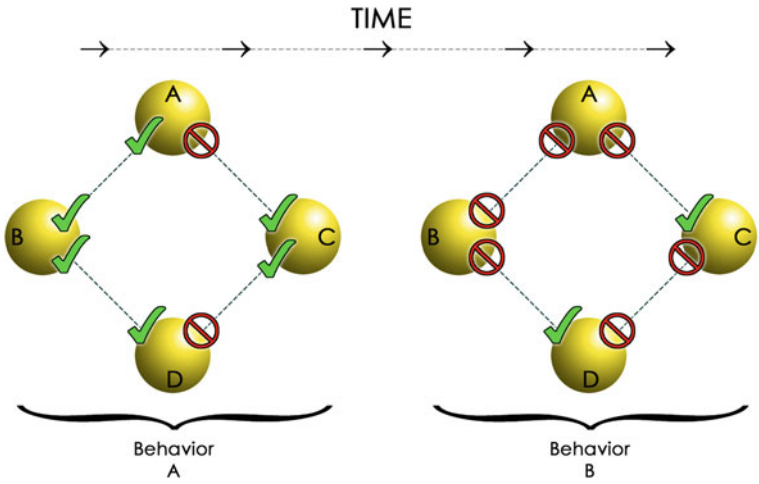

Fig. 11.2 Neuronal network interactions can change and shift across time and circumstance in a state-dependent manner (Silvanto and Pascual-Leone 2008). These variations will alter the effects and behavioral consequences of EM stimulation and are, accordingly, an important variable when considering neural function and enhancement capabilities

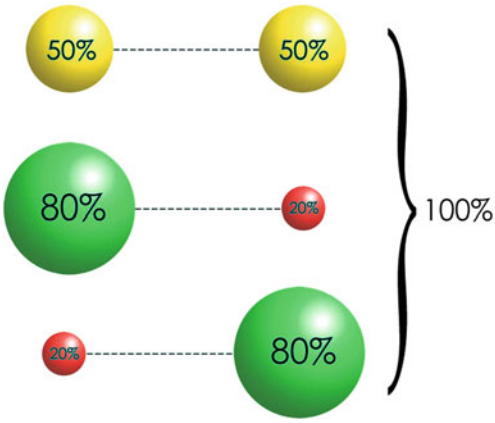

Fig. 11.3 Zero-Sum enhancement posits a finite but shifting amount of neural processing power. Any power gain to a discrete cerebral region will be matched by an equal power loss to one or several cerebral regions

When considering mental or performance enhancement, the term zero-sum refers to a situation whereby every gain in neural processing power somewhere in the brain is counterbalanced by an equal yet opposing loss of neural processing power elsewhere in the brain. Put another way, the zero-sum theory supposes the brain has a finite amount of processing power and that, in order for a physical or mental trait to be enhanced, processing power must be 'stolen' from other physical or mental traits. Assuming discrete neural regions interact to form functional neural networks, it is possible that finite processing power is network-specific and that EM stimulation serves to distribute this power within a given network

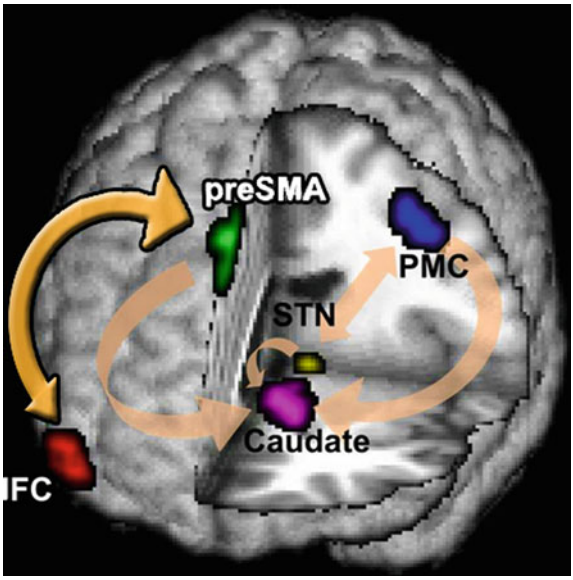

Fig. 11.4 A Granger (G-) causality analysis revealed a reciprocal G-causality relationship between the pre-supplementary motor area (pre-SMA) and the inferior frontal cortex (IFC). Image reprinted with permission of author (Duann et al. 2009)

(increasing activity in several regions, decreasing it in others) thereby generating measurable behavioral effects. In addition, concepts of correlated and anti-correlated networks (Fox et al. 2012) posit that modulation of activity in a given network may be mirrored in other, not-directly stimulated networks; the activity across which would be driven in the opposite direction.

Perhaps the best example of zero-sum processing is the often studied speed/accuracy trade off. Although there is some disagreement (Dutilh et al. 2011), many researchers have demonstrated that enhanced accuracy in reaction time (RT) tasks decreases response speed, and vice versa (van Veen et al. 2008; Bogacz et al. 2010). Although the majority of speed/accuracy research has utilized behavioral tasks, several researchers have utilized fMRI to demonstrate that, under conditions of emphasized speed, the pre-supplementary motor area (pSMA) demonstrates an increased BOLD signal whereas the lateral prefrontal cortex (LPFC) demonstrates a decreased BOLD signal. Conversely, under conditions of emphasized accuracy, the LPFC increases and the pSMA decreases BOLD signal (Forstmann et al. 2008; Ivanoff et al. 2008; Van Veen et al. 2008). Interestingly, functional connectivity data reveals a strong bidirectional functional connection between the pSMA and LPFC (Duann et al. 2009) suggesting the two regions are part of a singular 'speed-accuracy' neural network (Fig. 11.4). Accordingly, the differential activity between speed-accuracy conditions may indeed represent a shifting of finite, network-specific processing power.

As schematically represented in Fig. 11.1, a special instance of EM-mediated zero-sum enhancement is known as 'paradoxical facilitation' (Najib and Pascual-Leone 2011). Unlike a typical zero-sum protocol, whereby excitatory

stimulation is utilized to increase processing efficiency in a targeted neural region, enhancement through paradoxical facilitation may result from *inhibiting* the targeted region which, in turn, 'releases' a secondary, functionally connected neural site from suppressive control thereby generating a behavioral gain (Fig. 11.1d). Such effects can develop between nodes of a given network or across anti-correlated networks. For instance, functionally significant transcallosal inhibition has long been postulated between the bilateral parietal lobes in humans (see: Kinsbourne 2003). This means that when one parietal lobe is active (say, the right) it sends *inhibitory* signals to the contralateral parietal cortex (in this case, the left). Paradoxical facilitation predicts that if EM stimulation were used to inhibit the right parietal cortex, then this transcallosal inhibition would be broken and, as a result, the left parietal cortex would demonstrate enhanced function. Indeed, Hilgetag et al. (2001) verified this hypothesis. Following suppressive TMS to the parietal cortex, healthy subjects demonstrated decreased stimuli detection in the visual hemi-field contralateral to stimulation but enhanced stimuli detection in the hemi-field ipsilateral to stimulation (mediated by the released, unstimulated parietal cortex). Ultimately, such paradoxical facilitation illustrates the underlying principles of zero-sum enhancement.

An obvious difficulty when trying to determine if a functional enhancement is zero-sum concerns the identification and characterization of an associated functional detriment. Whereas some detriments are clearly related to the measured enhancement and, as such, are easy to elucidate (such as the trade-off between spatial and temporal resolution in visual tasks—Kortmann et al. 1999; Yeshurun and Levy 2003), many more are not obvious and may prove too subtle to catch the attention of researchers focused on a highly specific question. As an example, the dorsal lateral prefrontal cortex (DLPFC) contains connections to a myriad of neural regions (the orbitofrontal cortex, the thalamus, the hippocampus, the dorsal caudate nucleus, etc.—see: O'Reily et al. 2010) and has been implicated in a number of cognitive functions (working memory, intentionality, affect, decision making, etc.—see: Duncan and Owen 2000). Whereas this diversity allows for unique forms of enhancement, it also makes it quite challenging to determine if a secondary skill or mental function has been impaired. For instance, a researcher succeeding in improving a subject's working memory load by targeting the DLPFC may miss the fact that the same subject would now perform poorly on a gambling task or emotive recall task. Accordingly, although we will examine several possible examples of zero-sum enhancement later in this chapter, it is simply impossible to confirm whether or not these are conclusively zero-sum without the introduction of additional tasks or behavioral measures. Furthermore, it is worth noting that EM effects on network dynamics and distributed network activity may not necessarily lead to *any measurable* behavioral effects (Fox et al. 2012). In other words, zero-sum enhancement may not always be associated with measurable behavioral losses, but there may nonetheless be 'negative' or undesirable physiologic consequences that may manifest themselves in subsequent task performance or later predisposition for behavioral disruption.

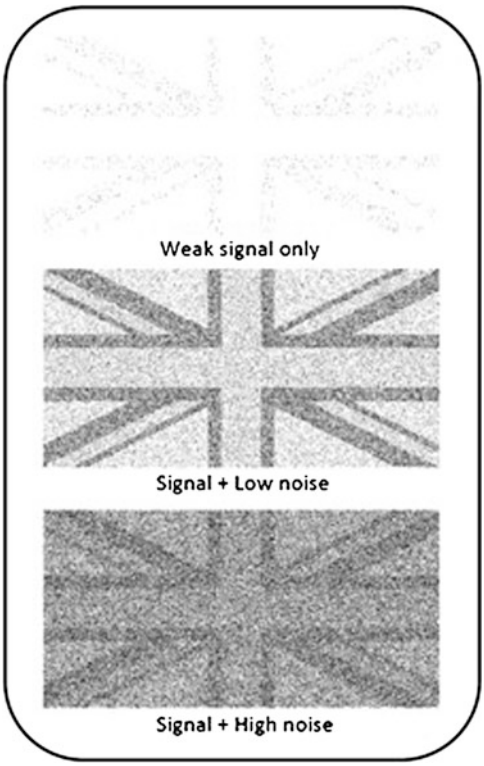

Fig. 11.5 Stochastic resonance posits that a signal which falls below sensory threshold (*top box*) can rendered identifiable with the addition of a small amount of random noise (*middle box*) and uncomprehensible with the addition of a lot of random noise (*bottom box*). Image reprinted with permission of author (Silvanto and Cattaneo In Press)

11.3.1 Stochastic Resonance Enhancement

Typically, when excessive levels of extraneous 'noise' are injected into a processing system, the result is an obfuscation of the original 'signal' and a concurrent impairment or breakdown of the system's function. However, *small* amounts of noise injected into a system, typically below a measurable threshold, may actually enhance low-level signals thereby improving stimuli detection within systems (Fig. 11.5; Gammaitoni et al. 1998). This use of noise to enhance signal detection, arguably another instance of paradoxical functional facilitation (Kapur 2011), is called stochastic resonance.

Any system with a measurable threshold is known as a bistable system. Put simply, bistable systems can exist in one of two states: either *on* or *off*. Biologically speaking, all known sensory modalities are bistable systems as, depending upon the strength of the external stimuli, sensations will either be felt (*on*) or go unnoticed (*off*). If a sinusoidal stimulus falls slightly below threshold (such as a quiet noise or dim light), injected wide-band noise can interact with this stimulus and form a more powerful cumulative signal. The amount of noise needed to optimally enhance sub-threshold stimuli is dependent upon two factors: the periodicity of the original sinusoidal signal and the Kramer's rate (the inverse of the rate with which the noise

alone will switch the system from *off* to *on*). When these two temporal values match, or 'resonate', the peaks of the original sub-threshold stimulus wave will increase to at-threshold levels thereby generating a clear signal. As can be imagined, when too much noise is added, the peaks of the original stimulus wave will grow to above-threshold levels and distort any registered signal.

Stochastic resonance may explain recent observations showing that, whereas high levels of TMS impair visual motion detection, low levels of stimulation actually facilitate the detection of weak motion signals in humans not detected at baseline measurements (Schwarzkopf et al. 2011). Reichenbach et al. (2011) similarly found that TMS delivered within a certain dynamic range enhanced neural reactivity to visual stimuli (as measured using electroencephalography)—stimulation above this range served only to impair neural reactivity.

Unlike zero-sum theory, stochastic resonance does not posit a finite amount of neural processing power. Instead, stochastic resonance enhances the power (or saliency) of low level signals thereby effectively lowering a system's threshold value. Under this hypothesis, enhancement does not occur via shifted or 'stolen' processing power, rather, enhancement occurs because stimuli are detected that would otherwise slip past recognition. Although experimental support for this theory remains scarce, its theoretical mechanisms offer sensible accounts for the findings of several studies examined later in this chapter.

An interesting implication of this conceptualization is that modified forms of EM stimulation that deliver true sinusoidal stimulation which can be synchronized to the stimulated person's own electroencephalographic activity may be particularly effective modes of enhancement. Methods such "synchronized EM stimulation" have been developed (Jin et al. In Press) and may offer unique tools to further examine concepts of stochastic resonance.

11.3.2 Entrainment Enhancement

In order for skills and memories to be available beyond initial acquisition, off-line informational processing and consolidation must occur. Although the mechanisms remain largely unknown, it has long been theorized that slow-wave sleep (SWS) facilitates at least part of this off-line consolidation (for review: Diekelmann and Born 2010). Electrophysiologically, SWS is characterized by global slow frequency oscillation ($\sim$0.75 Hz) and an endogenous DC potential shift (Achermann and Borbely 1998; Marshall et al. 2003). Although not identical, this type of neural pattern can be mimicked, or 'entrained', utilizing EM stimulation. In this particular instance, entrainment enhancement posits that if EM devices (for example tDCS) can be used to generate SWS neural patterns, then the brain will have more time to consolidate memories and, accordingly, memory will be enhanced.

Two studies have examined this supposition. Marshall et al. (2004) utilized tDCS during periods of SWS to increase slow wave oscillations and, effectively, prolong periods of SWS consolidation. They found that this entrainment led to a

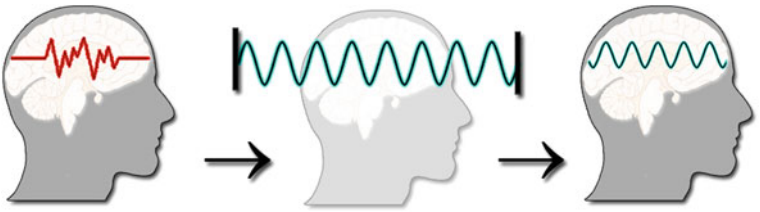

Fig. 11.6 Entrainment enhancement posits specific neural oscillations and processing states can be generated via external 'mimicking' by EM stimulation

better retention of specified declarative memories (word-pairs memorized immediately before sleep) with no detriment in the retention of a specified procedural memory (mirror tracing figures also presented immediately before sleep). In a separate study, Marshall et al. (2011) utilized tDCS during sleep to *disrupt* SWS and entrain neural patterns similar to those generated during rapid eye movement (REM) sleep. They found that strong tDCS during SWS led to a decreased retention of specified declarative memories (word-pairs memorized immediately before sleep).

Unlike zero-sum, which depends on a reallocation of neural resources within a given network, and stochastic resonance, which adds noise to lower threshold values, entrainment works by 'mimicking' neural oscillation (via external stimulation) thereby 'tricking' the brain into a natural state known to correlate with success in a particular skill or trait (Fig. 11.6). Although this type of enhancement has been exclusively explored thus far using SWS memory consolidation, there is no reason to assume EM stimulators cannot entrain brain states for any number of physical and/or mental skills. EEG-guided EM stimulation may enable such approaches (Thut and Pascual-Leone 2010) and, again, the use of synchronized EM stimulation (Jin et al. In Press) might offer particularly advantageous features.

11.4 Electromagnetic Enhancement: Empirical Evidence

Despite numerous popular press articles and general science television segments (Fox 2011; Hamzelou 2011; NOVA 2011), the totality of evidence supporting the enhancement capabilities of EM devices is rather small and there is still great debate concerning the true potential of enhancement using brain stimulation. To date, slightly over 80 studies have been published (42 using TMS and 41 using tDCS) aiming to enhance cognition or behavior in healthy subjects. In the following sections we summarize these studies and discuss their strengths and weaknesses. Overall, the available empirical data suggest that the growing excitement concerning EM neuroenhancement is somewhat premature, and that carefully designed and properly controlled studies are critically needed.

11.4.1 Motor Learning

Table 11.1 summarizes the 28 published studies applying EM stimulation to enhance motor function and motor learning in healthy individuals. Motor function constitutes the bulk of the published EM enhancement research to date. In 1989, only 4 years after the first commercially available TMS device was developed, Day et al. reported that a single TMS pulse delivered to the motor cortex immediately before a voluntary motor response could significantly delay reaction time (RT). Building upon this observation, Pascual-Leone et al. (1992a) found that single TMS pulses, depending on timing and intensity, could also *decrease* RT. The theory put forward by Pascual-Leone et al. was that the current induced by the TMS pulse synergistically enhanced the pre-movement build-up of motor cortical excitability and, thus, enabled earlier initiation of movement. Since then, researchers have utilized various stimulatory paradigms and behavioral procedures to demonstrate EM motor enhancement. However, experimental demonstration remains elusive and careful control of non-specific factors, such as startle or intersensory facilitation, is critical (Valldeoriola et al. 1998; Molinuevo et al. 2000). The shortening of RT appears, at least in part, to be secondary to such effects, which can be rather difficult to control for given the multi-modal nature of TMS or tDCS and the limitations of sham interventions (Broadbent et al. 2011; Merabet and Pascual-Leone 2010).

Much motor-related enhancement work has focused on applying TMS over the primary motor cortex (M1) (see Table 11.1). Many studies have demonstrated enhancement via the excitation of the motor output to a particular muscle in contralateral M1 (e.g—Kim et al. 2004; Tecchio et al. 2010). However, other studies demonstrate nearly identical enhancement via the *inhibition* of the motor output to homologous muscles in *ipsilateral* M1 (e.g—Kobayashi et al. 2009; Bashir et al. 2011). Such findings provide empirical support for the earlier discussed zero-sum 'paradoxical facilitation'. Ferbert et al. (1992) first demonstrated that stimulation of a primary motor cortex induces suppression of motor cortical outputs from the contralateral, unstimulated hemisphere. This interhemispheric inhibition is an example of the type of network modulations we discuss above and suggests that, following enhancement of activity in one motor cortex, there might be functional enhancement within the contralateral hand and disruption of performance with the ipsilateral hand. Such effects have indeed been reported (Chen et al. 1997; Cincotta et al. 2006). However, physiologic modulation is not always linked to measurable behavioral effects. In addition, Hanajima et al. (2001) demonstrated that interhemispheric facilitation, rather than suppression, can also be induced, dependant on the intensity of stimulation and the precise timing between stimuli. Therefore, as graphically illustrated in Fig. 11.1, variations in stimulation parameters can lead to quite different behavioral effects. Furthermore, in the context of pathologies (e.g. following a stroke), the balance of interhemispheric interactions can be shifted (Perez and Cohen 2009). Accordingly, the behavioral effects of such interventions may be altered or even reversed. In any case, in all these instances, it seems reasonable to assume zero-

Table 11.1 EM motor enhancement studies

Study	(n)	Region/s Stimulated	Protocol	Cognitive Domain / Task	Results	Enhancement
tDCS						
Nitsche et al. (2003)	80	Contralateral M1, Premotor Cortex, Lateral Prefrontal Cortex, or Medial Prefrontal	1 mA 15 min Online	Implicit Motor Learning: Serial Reaction Time Task (SRTT)	Anodal stim over M1 reduced RT during implicit learning block ~38% compared to sham (~55 ms differential vs ~40 ms differential). No effects at any other stim location.	Approx 15 ms RT
Anatal et al. (2004a)	42	Contralateral M1 or V5/MT+	1 mA 10 min Online	Visuomotor Accuracy: Tracking task	Anodal stim over M1 improved visuomotor performance ~89% compared to sham (17 vs 9 correct movements). Anodal stim over V5/MT+ improved visuomotor performance by ~78% compared to sham (16 vs 9 correct movements). Effects gone 5 minutes post stim.	Approx 7.5 Movements (out of 50)
Antal et al. (2004b)	12	Contralateral V5/MT+	1 mA 7 min Online	Visuomotor Accuracy: Tracking Task	Cathodal stim improved movement accuracy ~14% compared to baseline. Anodal stim improved movement accuracy ~4% compared to baseline. Effects gone 10 minutes post stim. No sham condition.	No Hard Numbers Available
Boggio et al. (2006)	8	Contralateral M1	1 mA 20 min Offline	Non-Dominant Hand Motor Performance: Jebsen-Taylor Hand Function Test (JTHF)	Anodal stim reduced JTHF time ~300% compared to sham (~3 second decrease from baseline vs ~0 second decrease). Typical task duration: 50 sec	Approx 3 Seconds

(continued)

Table 11.1 (continued)

Study	(n)	Region/s Stimulated	Protocol	Cognitive Domain / Task	Results	Enhancement
Vines et al. (2007)	7	Contralateral M1	1 mA 20 min Offline	Motor Sequence Learning: 4 Fingers, 5 Item	Cathodal stim increased left hand performance ~10% and decreased right hand performance ~3% compared to sham. Anodal stim increased right hand performance ~5% and decreased left hand performance ~1% compared to sham.	No Hard Numbers Available
Cogiamanian et al. (2007)	24	Contralateral M1	1.5 mA 10 min Offline	Non-Dominant Hand Motor Endurance: Voluntary Elbow Contraction	Anodal stim enhanced endurance time ~33% compared to sham (~80 seconds vs ~60 seconds). Both times were less than baseline (~100 seconds).	Approx 20 Seconds
Vines et al. (2008)	16	A—Contralateral M1 C—Ipsilateral M1 (Uni and Bi-Stim)	1 mA 20 min Offline	Non-Dominant Motor Sequence Learning: 4 Fingers, 5 Item	Bi-stim improved sequence accuracy ~25% compared to baseline. Sham improved sequence accuracy by ~12% compared to baseline.	No Hard Numbers Available
Reis et al. (2009)	24	Contralateral M1	1 mA 20 min Online	Novel Motor Skill Acquisition: Sequential Visual Isometric Pinch Task (SVIPT)	Anodal stim generated greater offline learning effects as compared to sham. 3-month follow up showed no retention difference, although the stim group maintained an overall better performance.	No Hard Numbers Available

(continued)

Table 11.1 (continued)

Study	(n)	Region/s Stimulated	Protocol	Cognitive Domain / Task	Results	Enhancement
Tanaka et al. (2009)	10	Contralateral M1	2 mA 10 min Online	Motor Strength: Leg Pinch Force	Anode stim increased pinch force between big and pointer toes ~600% compared to sham (~7 newton increase from baseline vs ~1 newton increase). Effects present 30 minutes post stim. Effects gone 60 minutes post stim.	Approx 6 Newtons
Hummel et al. (2010)	10 Elderly	Contralateral M1	1 mA 20 min Online	Motor Performance: Jebsen-Taylor Hand Function Test (JTHF)	Anodal stim reduced JTHF time ~300% compared to sham (~2 second decrease from baseline vs ~1 second increase) Typical task duration: 50 sec	Approx 20 Seconds
Tecchio et al. (2010)	44	Contralateral M1	1 mA 15 min Offline	Non-Dominant Motor Sequence Learning: 4 Fingers, 9 Item	Anodal stim increased consolidation of motor sequence ~11%, compared to only 5% with sham	Approx 6 Newtons
Williams et al. (2010)	19	A—Contralateral M1 C—Ipsilateral M1 (Bi-Stim only)	1 mA 40 min Online	Non-Dominant Motor Performance: Jebsen-Taylor Hand Function Test (JTHF)	Following 2 hours and 40 minutes of training, stim reduced JTHF time ~250% compared to sham (~5 second decrease from baseline vs ~2 second decrease) Typical task duration: 50 sec	Approx 3 seconds

(continued)

Table 11.1 (continued)

Study	(n)	Region/s Stimulated	Protocol	Cognitive Domain / Task	Results	Enhancement
Kang and Paik (2011)	11	A – Contralateral M1 C – Ipsilateral M1 (Uni- and Bi-Stim)	2 mA 20 min Online	Implicit Motor Learning: Serial Reaction Time Task (SRTT)	No difference between Uni-, Bi-, or Sham immediately following stimulation. 24 hours later, both uni- and bi-stim led to greater consolidation as compared to sham (~0 ms RT decrease vs ~25 ms RT decrease).	Approx 25 ms RT
Matsuo et al. (2011)	14	Contralateral M1	1 mA 20 min Offline	Motor Accuracy: Circle Drawing Task	Anodal stim improved circle deviation area ~15% compared to baseline (4.05 cm^2 vs 4.74 cm^2) and path length ~2% compared to baseline (50.2 cm vs 51.1 cm). Effects present 30 minutes post stim.	Approx 0.7 cm^2 area and 1 cm length
TMS						
Pascual-Leone et al. (1992a)	9	Bilateral M1	Single Pulse Variable Intensities Online	Motor Speed: Simple Reaction Time	Subthreshold stim delivered at 'Go' signal onset (both locations) decreased simple RT ~18% compared to baseline (~90 ms vs ~110 ms). At threshold stim delivered at 'Go' signal (ipsilateral location only) decreased simple RT ~20% compared to baseline (~88 ms vs ~110 ms)	Approx 20 ms RT

(continued)

Table 11.1 (continued)

Study	(n)	Region/s Stimulated	Protocol	Cognitive Domain / Task	Results	Enhancement
Pascual-Leone et al. (1992b)	5	Bilateral M1	Single Pulse Variable Intensities Online	Motor Speed: Simple Reaction Time w/ Multisensory Go Signals	Subthreshold stim delivered 5–10 ms post 'Go' signal onset (contralateral M1 only, all sensory modalities) decreased simple RT ~15% compared to baseline (~30 ms average). Suprathreshold stim delivered 5–10 ms post 'Go' signal onset (ipsilateral M1 only, all sensory modalities) decreased simple RT ~13% compared to baseline (~25 ms average).	Approx 27 ms RT
Terao et al. (1997)	8	Bilateral M1, Cz, or Pz	Single Pulse Variable Sub-threshold Intensities Online	Motor Speed: Simple Reaction Time	Stim delivered at 'Go' signal onset (all locations) decreased simple RT ~25% compared to baseline (~150 ms vs ~200 ms).	Approx 50 ms RT
Sawaki et al. (1999)	7	Bilateral M1	Single Pulse 90% rMT Online	Motor Speed: Simple and Go/No-Go Reaction Time	Stim delivered at 'Go' signal onset (both locations) decreased simple RT ~25% compared to baseline (~130 ms vs ~172 ms). Stim delivered 90 ms post 'Go' signal onset (both locations) decreased Go/No-Go RT ~18% compared to baseline (~180 ms vs ~219 ms).	Approx 40 ms RT

(continued)

Table 11.1 (continued)

Study	(n)	Region/s Stimulated	Protocol	Cognitive Domain / Task	Results	Enhancement
Kim et al. (2004)	15	Contralateral M1	10 Hz 2 Second Bursts 80% rMT Online	Motor Sequence Learning: 4 Fingers, 7 Item	Stim increased overall accuracy ~17% compared to sham (~135 correct responses vs ~115 correct responses). Stim also decreased execution time ~14% compared to sham (~290 ms vs ~340 ms).	Approx 20 key presses (in 40 seconds) and 50 ms (per sequence).
Kobayashi et al. (2004)	16	Bilateral M1	1 Hz 600 pulses 90% rMT Offline	Motor Sequence Learning: 4 Fingers, 4 Item	Following sequence performance plateau, stim decreased sequence execution time (ipsilateral hand only) ~8% compared to sham (~185 ms average vs ~200 ms average). Effect present 10 min post stim.	Approx 15 ms RT
Gregori et al. (2005)	10	Contralateral M1, premotor cortex, or supplementary motor cortex.	50 Hz 3 pulse bursts Variable Intensities Online	Motor Sequence Learning: Upper Limb, 5 Item	Stim had no effect on motor sequence. However, subthreshold stimulation delivered before the 'Go' signal (all locations) decreased time-to-start duration ~23% compared to sham (~180 ms vs ~235 ms). Suprathreshold stimulation delivered before the 'Go' signal (all locations) decreased time-to-start duration ~15% compared to sham (~200 ms vs ~235 ms).	Approx 45 ms RT

(continued)

Table 11.1 (continued)

Study	(n)	Region/s Stimulated	Protocol	Cognitive Domain / Task	Results	Enhancement
Dafotakis et al. (2008)	18	Bilateral M1	1 Hz 1600 pulses 100% rMT Offline	Motor Speed: Finger and Hand Tapping	Stim increased finger tapping frequency in ipsilateral hand ~7% compared to baseline (~5.4 Hz vs ~5 Hz). Stim increased hand tapping frequency in ipsilateral hand ~8% (~6 Hz VS ~5.5 Hz). No sham condition.	Approx 0.5 Hz (task duration not given)
(Boyd and Linsdell 2009)	32	Contralateral Premotor Cortex	5 Hz 15 min 120% rMT Offline	Motor Consolidation: Tracking Task	Following 5 days of training, stim decreased the root mean square error ~10% compared to sham (~18 RMSE vs ~20 RMSE	No Hard Numbers Available
Galea et al. (2009)	30	Bilateral DLPFC	iTBS 80% aMT Offline	Implicit Motor Learning: Serial Reaction Time Task (SRTT)	Right DLPFC stim decreased retention phase RT ~15% compared to baseline (~275 ms vs ~325 ms) Left DLPFC stim decreased retention phase RT ~9% compared to baseline (~250 ms vs ~275 ms)	Approx 35 ms RT
Kobayashi et al. (2009)	24	Bilateral M1	1 Hz 1600 pulses 90% rMT Offline	Motor Sequence Learning: 4 Fingers, 4 Item	Stim decreased execution time in ipsilateral hand ~7% compared to sham (~265 ms vs ~285 ms) Effect present only in second test block. Effect gone ~2 minutes post stim	Approx 20 ms RT

(continued)

Table 11.1 (continued)

Study	(n)	Region/s Stimulated	Protocol	Cognitive Domain / Task	Results	Enhancement
Bashir et al. (2011)	10	Ipsilateral M1	1 Hz 1600 pulses 90% rMT Offline	Motor Speed: Simple Reaction Time	Stim decreased RT in ipsilateral hand by ~10% compared to sham (~340 ms vs ~380 ms)	Approx 40 ms RT
Buetefisch et al. (2011)	12 (middle aged)	Left M1 (bilateral motor task)	1 Hz 900 pulses 90% rMT Offline	Motor Accuracy: Pointing Task	Stim increased small target 'hit' percentage ~7% for the ipsilateral hand compared to baseline (~12 vs ~10.5). Stim increased medium target 'hit' percentage ~6% for the contralateral hand compared to baseline (~18 vs ~16.5).	Approx 1.5 'hits' (out of 20)
Teo et al. (2011)	13	Contralateral M1	iTBS 90%aMT Offline	Motor Speed: Thumb Acceleration	Stim increased thumb acceleration ~43% compared to sham (~2.5 g vs ~1.75 g)	Approx 0.75 g force

sum mechanisms: ipsilateral motor behaviors are enhanced in balance with worsening motor behaviors contralateral to the stimulated motor cortex (or vice versa). Unfortunately, careful quantitative assessment of such relations are lacking in the studies to date.

Interestingly, several studies are clearly not consistent with the zero-sum principle. For example, Gregori et al. (2005) demonstrated a decrease in RT with a 50 Hz burst of TMS delivered at the 'go' signal over both contralateral M1, premotor cortex, and the supplementary motor cortex. This location-independent RT enhancement is suggestive of either strikingly complex network dynamics (Fig. 11.2b) or stochastic resonance. In the later case, the 'noise' added by the TMS burst, regardless of location, may serve to enhance the salience of the 'go' signal thereby generating quicker subject responses.

Regardless of the mechanisms at play, there does seem to be evidence suggesting the motor enhancement potentialities of EM stimulation. However, the true functional significance of this enhancement is debatable. First, a lot of the studies simply report a speeding up of performance—whether or not this speed results in better or more accurate performance is largely unknown. Furthermore, the reported effect size of faster performance is often discrete. A simple average of all RT studies shows a mean shortening of $\sim$32 ms. Under certain circumstances, 32 ms can mean the difference between success and failure (consider a gunfight in the old west or a military pilot in a dog-fight), but it is difficult to come up with many every day activities where 32 ms is decisively important. Similarly, although several studies do demonstrate larger performance enhancements (Friedhelm et al. 2010; Williams et al. 2010), both the overall duration and sustainability of these enhancements is unknown.

Simply speeding up rather low-difficulty motor performance, while potentially of interest, does not establish the feasibility of EM neuroenhancement for more complex motor behaviors. Although some studies have explored these issues, assessing the impact of EM stimulation on motor learning and visuomotor accuracy, the results have been mixed and are somewhat difficult to interpret. For example, Reis et al. (2009) reported increased offline motor learning effects following tDCS, however, no effect remained at a 3-month follow-up. This leaves open many questions regarding timing and duration concerns. To confound matters, although reporting varied performance and error transformation scores, many researchers examining complex motor learning do not report hard scores or values (see Table 11.1). As such, determining true enhancement effect sizes is difficult at best, impossible at worst. Additional studies geared toward examining non-RT motor enhancements are needed and should report of both duration and comprehensive raw-score measurements.

11.4.2 Language

Table 11.2 summarizes the 21 published studies examining the potential of EM stimulation to enhance language abilities in healthy subjects. When considering language and the brain, two neural regions typically stand out: Broca's area (linked

Table 11.2 EM language enhancement studies

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
tDCS						
Iyer et al. (2005)	30	Left DLPFC	2 mA 20 min Offline	Verbal Fluency: Word Generation Task	Anodal stim increased number of words starting with a specific letter generated in 90 seconds ~2 compared to sham and cathodal stim (No Hard Numbers Available)	Approx 2 Words (in 90 seconds)
(Cerruti and Schlaug 2008)	18	Left DLPFC	1 mA 20 min Offline	Verbal Association: Remote Associates Test (RAT)	Anodal stim increased the number of correct RAT answers ~12% compared to sham and cathodal stim (~9 vs ~8 for both sham and cathode)	Approx 1 Associative Word (out of 16)
Floel et al. (2008)	19	Wernicke	1 mA 20 min Online	Language Learning: Pseudo-Word Paired Association Task	Anodal stim increased the number of correct responses ~5% compared to sham and cathodal stim (~105 correct responses vs ~100 correct responses). Effects gone 1 week post stim.	Approx 5 Pseudo-Words (out of 120)
Sparing et al. (2008)	15	Wernicke	2 mA 7 min Offline	Speech Facilitation: Picture Naming Task	Anodal stim decreased picture naming latency ~5% compared to sham (~505 ms vs ~530 ms). Effects gone after 5 minutes	Approx 25 ms RT
De Vries et al. (2009)	38	Broca	1 mA 20 min Offline	Grammar Learning: Implicit Grammatical Association Task	Anodal stim increased the number of detected low resemblance, non-grammatical violations ~25% compared to sham (~10 correct responses vs ~8 correct responses).	Approx 2 Words (out of 25)

(continued)

Table 11.2 (continued)

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
Feronani et al. (2010)	12	Left DLPFC	2 mA 8 min Offline	Speech Facilitation: Picture Naming Task	Anodal stim decreased picture naming latency ~6% compared to sham (~665 ms vs ~705 ms)	Approx 40 ms RT
Ross et al. (2010)	15	Bilateral Temporal Lobe	1.5 mA 15 min Online	Speech Facilitation: Proper Name Recall Task	Anodal stim over the right temporal lobe increased proper name recall ~40% compared to sham (~21 vs ~15)	Approx 6 Proper Names (out of 88)
Cattaneo et al. (2011)	10	Broca	2 mA 20 min Offline	Verbal Fluency: Word Generation Task	Anodal stim increased number of words starting with a specific letter generated in 60 seconds ~23% compared to sham (~16 words vs ~13 words). Anodal stim increased number of words fitting a particular category generated in 60 seconds ~29% compared to sham (~22 words vs ~17 words).	Approx 4 Words (in 60 seconds)
Holland et al. (2011)	10	Left DLPFC	2 mA 20 min Online	Speech Facilitation: Picture Naming Task	Anodal stim decreased picture naming latency ~3% compared to sham (~800 ms vs ~780 ms)	Approx 20 ms RT

(continued)

Table 11.2 (continued)

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
TMS						
Topper et al. (1998)	65 males	Wernicke	Single-Pulse 35-95% machine output Online	Speech Facilitation: Picture Naming Task	55% intensity stim 1000 ms pre-stimulus decreased picture naming latency ~9% compared to baseline (~590 ms vs ~650 ms) 55% intensity stim 500 ms pre-stimulus decreased picture naming latency ~7% compared to baseline (~605 ms vs ~650 ms) 35% intensity 500 ms pre-stimulus decreased picture naming latency ~15% compared to baseline (~550 ms vs ~650 ms)	Approx 60 ms RT
Mottaghy et al. (1999)	15	Wernicke	20 Hz 2 second bursts 55% machine output Online	Speech Facilitation: Picture Naming Task	Stim decreased picture naming latency ~9% compared to control (~480 ms vs ~530 ms).	Approx 50 ms RT
Sparing et al. (2001)	16	Wernicke	20 Hz 40 pulses 55% machine output Offline	Speech Facilitation: Picture Naming Task	Stim immediately decreased picture naming latency ~5% compared to sham (~530 ms vs ~560 ms) Effects gone after 2 minutes	Approx 30 ms RT

(continued)

Table 11.2 (continued)

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
Cappa et al. (2002)	9	Bilateral DLPFC	20 Hz 500 ms trains 90% rMT Online	Speech Facilitation: Picture Naming Task	Stim over left DLPFC decreased verb naming latency ~7% compared to sham (~850 ms vs ~910 ms)	Approx 60 ms RT
Drager et al. (2004)	20	Broca	1 Hz 600 pulses 100% rMT Offline	Speech Recognition: Visual and Auditory Object Matching Task	Following adjustments, stim over Broca decreased RT ~3% compared to baseline (~495 ms vs ~510 ms).	Drager et al. (2004)
Andoh et al. (2006)	12	Wernicke	1 Hz 10 min 110% rMT Offline	Speech Recognition: Non-Native Sentence Recognition Task	Stim decreased RT latency ~16% compared to sham (~1025 ms vs ~1225 ms)	Approx 200 ms RT
(Mottaghy et al. 2006) EXP 1	41 males	Wernicke	Single-Pulse 35-95% machine output Online	Speech Facilitation: Picture Naming Task	Lower intensity stim (<75%) 1000 ms pre-stimulus decreased picture naming latency ~8% compared to baseline. Lower intensity stim (<75%) 500 ms pre-stimulus decreased picture naming latency ~7% compared to baseline.	No Hard Numbers Available
(Mottaghy et al. 2006) EXP 2	36 males	Wernicke	20 Hz 2 second bursts 35-55% machine output Online	Speech Facilitation: Picture Naming Task	55% intensity stim immediately pre-stimulus decreased picture naming latency ~10% compared to baseline. Effects gone after 2 minutes	No Hard Numbers Available

(continued)

Table 11.2 (continued)

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
Andoh et al. (2008) EXP 1	14 males	Wernicke	1 Hz 600 pulses 100% rMT Offline	Speech Recognition: Native and Non-Native Sentence Recognition Task	Stim decreased native sentence RT latency ~6% compared to sham (~950 ms vs ~1010 ms)	Approx 60 ms RT
Andoh et al. (2008) EXP 1	14 males	Wernicke	iTBS 90% aMT Offline	Speech Recognition: Native and Non-Native Sentence Recognition Task	Stim decreased nonnative sentence RT latency ~8% compared to sham (~1035 ms vs ~1125 ms)	Approx 90 ms RT
Harpaz et al. (2009)	11	Bilateral Wernicke	10 Hz 500 ms bursts 100% rMT Online	Lexical Ambiguity Task	Stim over left Wernicke increased dominant word meaning recognition accuracy ~2% compared to sham. Stim over right Wernicke increased subordinate word meaning recognition accuracy ~6% compared to sham.	No Hard Numbers Available
Cotelli et al. (2010)	13 elderly	Bilateral DLPFC	20 Hz 500 ms bursts 90% rMT Online	Speech Facilitation: Picture Naming Task	Stim over either DLPFC decreased verb naming latency ~9% compared to sham (~980 ms vs ~1080 ms)	Approx 100 ms RT

to speech production) and Wernicke's area (linked to speech comprehension). Accordingly, these two areas are the two most targeted by researchers hoping to enhance language skills in healthy human subjects.

Stimulation over the speech production region can interfere with and even arrest speech production (Pascual-Leone et al. 1991). However, several studies do suggest that less intense stimulation, for example anodal tDCS over Broca's area, may actually increase language learning and production, most likely due to active neural priming (De Vries et al. 2009; Cattaneo et al. 2011).

More robust and replicated results have come from stimulation over Wernicke's area. Several studies have demonstrated that stimulation over this region can decrease picture naming speed (Mottaghy et al. 1999; Sparing et al. 2001; Cappa et al. 2002). Similar to the above discussed motor paradigms, these faster RTs may be attributable to increased neural processing power engendered by facilitatory stimulation (zero-sum). In this case, as strong bi-directional connections have been established (*arcuate fasciculus*; see Rilling et al. 2008), it might be that disruption of Wernicke's area serves to 'free up', or facilitate, function of Broca's area thereby leading to increased speech production. Despite this enhancement, however, the initial disruption to Wernicke's area may prove detrimental to the comprehension and online monitoring of the speech being produced. Conversely, perhaps enhancement effects are being generated directly at Wernicke's, whereby faster interpretation and comprehension of the given task is the source of the reduced RTs. Similarly, this increase in comprehension may require additional processing power obtained via the 'locking up', or inhibition, of Broca's thereby leading to less intelligible vocal responses. Either way, it is feasible to envision several scenarios whereby the reported enhanced RTs may be offset by concurrent detriments. However, conclusively determining whether or not a zero-sum detriment is present may prove a difficult task seeing as Wernicke's region is functionally connected to varied neural regions affecting varied behaviors (including the inferior parietal lobule, implicated in emotional and sensory interpretation, and the supplementary motor area, implicated in motor planning and bimanual control—Catani et al. 2005; Powell et al. 2006). Accordingly, a good first step for future research would be to carefully monitor and assess unique aspects of linguistic function (comprehension, production, monitoring, etc.), although this may not always reveal a zero-sum relationship.

Several studies demonstrate a nearly identical RT speed improvement with subthreshold single pulses or pulse bursts delivered to Wernicke's area shortly before stimulus presentation (Topper et al. 1998; Mottaghy et al. 2006). This enhancement might be perhaps more consistent with of stochastic resonance than zero-sum.

Irrespective of mechanism, there does seem to be replicated evidence for EM stimulation language enhancement. Stimulation over Wernicke's area and other frontal regions can decrease verbal RTs by $\sim$60 ms and, under certain circumstances, enhance verbal memory by several words. Unfortunately, as before, there is no conclusive evidence regarding the duration of these effects. Accordingly, it remains unclear if these enhancements would remain stable or if continuous

stimulation would be required to maintain performance levels. In addition, as many verbal tasks (e.g—learning a novel language) do not have an inherent performance ceiling, it is difficult to deduce if the reported enhancements would be important outside the laboratory. Finally, the importance of increased RTs with regards to language production and comprehension remains uncertain. Although certainly interesting, does the ability to speak faster truly confer enhancement? Although not reported, it is not difficult to envision a scenario whereby enhanced speed would come at the cost of other linguistic functions. Accordingly, without systematic and careful assessment of complete linguistic processes following stimulation, it remains unclear whether RT enhancement will prove to be beneficial in a translational effort.

11.4.3 Working Memory

Table 11.3 summarizes the 12 published studies applying EM stimulation to enhance working memory (WM). The neurobiological substrate of WM is an ongoing topic of research; however, prefrontal regions are broadly believed to be critically involved. As such, nearly all WM enhancement research has focused on modulation of the dorsolateral prefrontal cortex (DLPFC).

Several studies have demonstrated and replicated enhanced n-back performance following anodal tDCS over the left DLPFC (e.g—Ohn et al. 2008; Zaehle et al. 2011). In addition, high frequency TMS over the parietal cortex has been linked to decreased RT and increased retention during visual delayed match-to-sample tasks (e.g—Luber et al. 2007; Hamidi et al. 2008). These sets of studies, utilizing facilitatory stimulation, certainly appear to fall under the zero-sum enhancement theory, although no concurrent detriments were sought out or reported.

As in both the motor and language enhancement sections, several studies appear to generate similar enhancement via stochastic resonance (Yamanaka et al. 2010; Hannula et al. 2010; Savolainen et al. 2011). As before, these studies demonstrate that single pulses or short pulse bursts delivered to varied neural regions shortly following the presentation of a stimulus can enhance RTs comparable to the enhancements generated following longer protocols.

Mechanisms aside, the WM enhancement effects appear largely to relate to stimulus RTs. Although these decreased RTs are impressive, time is not paramount when considering WM. Instead, WM tends to be defined by *capacity*. Accordingly, it is somewhat disheartening to see only a handful of studies reporting an enhanced WM capacity following stimulation, and the effect sizes of these studies are no more than those found utilizing caffeine or other non-pharmaceutical stimulants (Smillie and Gokcen 2010). Again, we are forced to ask, what importance does a couple dozen milliseconds confer with regard to WM? Future experiments should continue to explore issues of capacity and storage duration, as desired WM enhancement would most likely involve remembering more information for a longer period of time; not merely quicker RTs.

Table 11.3 EM working memory enhancement studies

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
tDCS						
Fregni et a.l (2005)	15	A—Left DLPFC C – Right DLPFC	1 mA 10 min Online	Visual 3-Back Task	Stim increased number of correct responses ~10% compared to sham (~22 vs ~20). Stim decreased number of errors ~28% compared to sham (~5 vs ~7)	Approx 4 numbers (out of 30)
Ferrucci et al. (2008)	17	DLPFC (no specified laterality)	2 mA 15 minutes Offline	Numerical Delayed-Match-To-Sample Task	Cathodal stim decreased RT ~6% compared to sham (~625 ms vs ~665 ms)	Approx 40 ms RT
Ohn et al. (2008)	15	Left DLPFC	1 mA 20 min Online	Verbal 3-Back Task	Anodal stim increased correct answer accuracy ~14% compared to sham (~24 vs ~21) Effect present 30 min post-stim	Approx 3 Letters (out of 30)
Andrews et al. (2011)	10	Left DLPFC	1 mA 10 min Offline	Forward/Backward Digit Span Task	Anodal stim (with concurrent n-back practice) increased forward digit span ~7% compared to baseline (~14 vs ~13) Anodal stim (with concurrent n-back practice) increased backward digit span ~11% compared to baseline (~10 vs ~9) No effects compared to sham	Approx 1 number (span)
Mulquiney et al. (2011)	10	Left DLPFC	1 mA 20 min Online	Visual 2-Back Task	Anodal stim decreased RT for correct responses ~2% compared to sham (~2830 ms vs ~2880 ms)	Approx 50 ms RT
Zaehle et al. (2011)	16	Left DLPFC	1 mA 15 min Offline	Visual 2-Back Task	Anodal stim decreased RT for correct responses ~35% compared to baseline. Anodal stim increased RT for incorrect responses ~10% compared to baseline.	No Hard Numbers Available
TMS						
Luber et al. (2007)	44	Midline Parietal Cortex	5 Hz 7 second bursts 100% rMT Online	Alphabetic Delayed-Match-To-Sample Task	Stim during retention phase decreased 6-letter grid RT ~11% compared to sham (~625 ms vs ~700 ms) Stim during probe phase increased 1-letter grid recall accuracy ~7% compared to sham (~31 vs ~29)	Approx 2 letters (out of 32) and 75 ms RT

(continued)

Table 11.3 (continued)

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
Hamidi et al. (2008)	24	Superior Parietal Lobule	10 Hz 3 second bursts 110% rMT Online	Spatial Delayed-Match-To-Sample Task	Stim during retention phase decreased RT ~2$ compared to sham (~950 ms vs ~970 ms)	Approx 20 ms RT
Preston et al. (2009)	32	Left DLPFC	5 Hz 250 pulses 100% rMT Offline	Alphabetic Delayed-Match-To-Sample Task	Stim decreased correct response RT ~14% compared to sham (~874 ms vs ~1014 ms)	Approx 140 ms RT
Hannula et al. (2010)	6	Middle Frontal Gyrus	Single Pulse 120% rMT Online	Tactile Stimuli Discrimination WM Task	Stim delivered 300 ms post first stimulus (over MFG regions with stong connections to primary somatosensory cortex) decreased RT ~15% compared to baseline (~730 ms vs ~860 ms)	Approx 130 ms RT
Yamanaka et al. (2010)	52	Right Parietal Cortex	5 Hz 6 second bursts 100% rMT Online	Spatial Delayed-Match-To-Sample Task	Stim during retention phase decreased RT ~7% compared to sham (~800 ms vs ~865 ms)	Approx 65 ms RT
Savolainen et al. (2011)	12	Middle Frontal Gyrus	Single Pulse 120% rMT Online	Tactile Stimuli Discrimination WM Task	Stim delivered 300 ms post first stimulus (in the presence of a tactile distractor) decreased RT ~4% compared to baseline (~770 ms vs ~800 ms)	Approx 30 ms RT

11.4.4 Executive Functions

Table 11.4 summarizes the 9 published studies in which EM stimulation has been applied to enhance executive functions. Executive functions (EF) can be loosely defined as a collection of neural processes influencing cognitive planning, flexibility, motivation, will-power, self-control, and self-regulation, and all are tied largely to the prefrontal lobes and their connected distributed brain networks. Nearly every reported study examining EF has targeted the DLPFC in a bid to enhance focused attention, willpower, or self-control. Every study reported in Table 11.4 has utilized facilitatory stimulation, most likely in a zero-sum attempt to increase local processing efficiency. However, as we have seen before, other theoretical mechanisms are worth considering and thus other experimental designs with less restricted conceptual frameworks should be conducted.

A look at Table 11.4 reveals a small consensus concerning the ability of EM stimulation to enhance inhibitory processes. Jacobson et al. (2011), Hsu et al. (2011) have both shown offline tDCS can reduce RT and increase inhibitory control during a clinical stop-signal task, and Fecteau et al. (2007) demonstrated a similar effect utilizing a a gambling task more akin to everyday decision making and risk taking. However, beyond this, there has not been much data replication or consensus.

11.4.5 General Memory and Learning

Table 11.5 summarizes the 14 published studies applying EM stimulation to enhance learning capacity in more generic terms. A diversity of approaches has been utilized thereby making it rather difficult to unearth a pattern regarding stimulatory condition, mechanisms, and outcome. Furthermore, some studies appear to directly contradict others. For instance, Boggio et al. (2009) reported decreased 'false memories' utilizing excitatory tDCS over the temporal lobe whereas Gallate et al. (2009) reported a nearly identical effect utilizing *inhibitory* TMS over the same region. (Schutter and van Honk 2006) reported an increase in visual memory utilizing a long-term (zero-sum) modulation whereas Sauseng et al. (2009) reported similar findings utilizing short burst (stochastic resonance) interference. We mention this not to diminish anyone's findings, but to call attention to the fact that several seemingly disparate approaches appear to be generating similar results. Perhaps this is reflective of a stochastic resonance-like effect: in these cases, simply adding noise or energy into the system, no matter the form, might be enough to generate enhanced behaviors. Unfortunately, we are left with far too many unanswered questions, highlighting the need for better powered and controlled experiments.

The study by Marshall et al. (2004) deserves special mention as the first (and, sadly, only) utilization of entrainment enhancement logic we were able to find.

Table 11.4 EM executive functions enhancement studies

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
tDCS						
Fecteau et al. (2007)	36	A—Right DLPFC C—Left DLPFC	2 mA 15 min Online	Decision Making: Gambling Task	Stim increased number of low-risk choices ~12% compared to sham (~93 vs ~83).	Approx 10 low-risk choices (out of 100)
Dockery et al. (2009)	24	Left DLPFC	1 mA 15 min Online	Planning: Towers of London Task	Cathodal stim during acquisition phase reduced RT ~11% compared to sham (~7.8 sec vs ~8.7 sec) Anodal stim during recall phase reduced RT ~18% compared to sham (~5.6 sec vs ~6.8 sec) Anodal stim during recall phase increased accuracy ~3% compared to sham. Typical RT: 7.5 sec	Approx 1 second
Hsu et al. (2011)	14	Pre-Supplementary Motor Area	1.5 mA 10 min Offline	Inhibition: Stop Signal Task	Cathodal stim increased number of correct 'stops' (inhibited responses) ~10% compared to sham (~32 stops vs ~29 stops)	Approx 3 stops (out of ~48)
Jacobson et al. (2011)	11	Inferior Frontal Gyrus	1 mA 10 min Offline	Inhibition: Stop Signal Task	Anodal stim decreased stop signal RT ~13% compared to sham (~223 ms vs ~256 ms)	Approx 30 ms RT
TMS						
Boroojerdi et al. (2001)	16	Left DLPFC	5 Hz 10 second bursts 90% rMT Online	Analogs Reasoning: Geometric Shape Matching Task	Stim decreased simultaneous analogs shape identification RT ~10% compared to sham(~1900 ms vs ~2100 ms) Stim decreased sequential analogs shape identification RT ~8% compared to sham (~1100 ms vs ~1200 ms)	Approx 150 ms RT

(continued)

Table 11.4 (continued)

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
Vanderhasselt et al. (2006a)	22 females	Right DLPFC	20 Hz 1,560 pulses 110% rMT Offline	Attentional Shift: Auditory Set Switching task	Stim reduced auditory task switching speed ~21% compared to baseline (~262 ms vs 332 ms)	Approx 70 ms RT
Vanderhasselt et al. (2006b)	28 females	Left DLPFC	10 Hz 1,560 pulses 110% rMT Offline	Inhibition: Stroop Task	Stim reduced congruent response time ~5% compared to baseline (~416 ms vs ~436 ms) Stim reduced incongruent response time ~6% compared to baseline (~424 ms vs ~450 ms)	Approx 23 ms RT
Hwang et al. (2010)	17	Left DLPFC	10 Hz 900 pulses 90% rMT Offline	Inhibition: Connor's Continuous Performance Task	Stim reduced 4 second inter-stimulus interval commission errors ~17% compared to sham (~5 errors vs ~6 errors)	Approx 1 errors (out of 12)
Vanderhasselt et al. (2010)	20 females	Left DLPFC	10 Hz 1,560 pulses 110% rMT Offline	Task Preparation: Dual Audio-Visual Distracter Reaction Task	Stim reduced decision time for endogenous visual task in the presence of an auditory distracter ~9% compared to baseline (~264 ms vs ~288 ms)	Approx 24 ms RT

Table 11.5 EM general memory and learning enhancement studies

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
tDCS						
Kincses et al. (2003)	22	Left PFC	1 mA 10 min Online	Implicit Learning: Probabilistic Classification Task	Anodal stim increased correct classification ~14% compared to sham (~8 correct vs ~7 correct)	Approx 1 classification (out of 10)
Marshall et al. (2004)	30 males	A –Left and Right DLPFC	0.26 mA/cm^2 15 seconds on / 15 seconds off for 30 minutes Offline	Declarative Memory Consolidation: Verbal Paired Association Learning Task	Stim during 90 minutes of sleep enhanced word retention ~9% compared to sham (~39 words vs ~36 words)	Approx 3 words (out of 46)
Boggio et al. (2009)	30	A – Left Anterior Temporal Lobe C – Right Anterior Temporal Lobe (Uni – and Bi-Stim)	2 mA 10 min Online	False Memories: Categorical Word Memorization Task	Bilateral stim decreased the number of 'false memories' (recall errors) ~100% compared to unilateral stim (~1 error vs ~2 errors) and ~400% compared to sham (~1 error vs ~4 errors)	Approx 3 words (out of 9)
Chi et al.(2010)	36	Right Anterior Temporal Lobe	2 mA 13 min Online	Visual Memory: Geometric Shape Memorization Task	Left cathodal / right anodal stim decreased the number of correct answer omissions ~60% compared to sham (~2 omissions vs ~5 omissions)	Approx 3 shapes (out of 24)
Clark et al. (2010)	96	Right Inferior Frontal Cortex	2 mA 30 min Online	Novice Learning: Threat Assessment Task	Anodal stim (delivered during training) increased number of correct threat assessments on a post training-test ~63% compared to control (~13 correct vs ~8 correct)	Approx 5 assessed threats (out of 50)
Kadosh et al. (2010)	15	A – Right Parietal Lobe C – Left Parietal Lobe	1 mA 20 min Online	Numerical Competence: Pseudo-Number Paired Association Task	6 days of stim (delivered during training) increased incongruent stroop task RT(a measure of automatic numerical processing) ~100% compared to sham (~140 ms vs ~70 ms)	Approx 70 ms RT

(continued)

Table 11.5 (continued)

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
Bullard et al. (2011)	34	Near F8	2 mA 30 min Online	Novice Learning: Threat Assessment Task	Anodal stim (delivered during training) increased number of correct threat assessments on a post training-test ~115% compared to baseline (~72 correct vs ~35 correct)	Approx 37 assessed threats (out of 100)
Floel et al. (2011)	20 elderly	Right Temporo-Parietal Cortex	1 mA 20 min Online	Object Location Learning Task	Anodal stim increased free-recall correct responses ~120% compared to sham (~11 correct vs ~5 correct)	Approx 6 building locations (out of 45)
TMS						
Kohler et al. (2004)	12	Left Inferior Prefrontal Cortex	7 Hz 4 pulse bursts 100% rMT Online	Episodic Memory: Categorical Word Recognition Task	Stim increased number of correct 'high confidence' responses ~4% compared to baseline (~238 hits vs ~229 hits)	Approx 9 words (out of 360)
Kirschen et al. (2006)	30	Left Inferior Parietal Lobule	3 pulses 120% rMT Online	Phonological Memory: Pseudo-Word Memorization Task	Stim decreased correct 'lure' probe response time ~9% compared to sham (~895 ms vs ~925 ms)	Approx 30 ms RT
Schutter and van Honk (2006)	11	Left Orbito Frontal Cortex	1 Hz 20 min 80% rMT Offline	Visual Memory: Emotive Face Memorization Task	Stim increased memory for 'happy' emotional faces compared to sham.	No Hard Numbers Available
Gallate et al. (2009)	20	Left Anterior Temporal Lobe	1 Hz 10 min 90% rMT Offline	False Memories: Categorical Word Memorization Task	Stim decreased the number of 'false memories' (recall errors) ~33% (~2 errors vs ~1 error)	Approx 1 word (out of 9)
Sauseng et al. (2009)	7	Bilateral Posterior Parietal Cortex	10 Hz 9 pulse bursts 110% rMT Online	Visual Memory: Bilateral Field Color Memorization Task	Stim to hemisphere ipsilateral to relevant stimuli increased short-term visual memory capacity ~15% compared to sham (~3.1 items vs ~2.7 items)	Approx 0.4 items
Gagnon et al. (2011)	11	Left DLPFC	Two pulses 90% rMT Online	Episodic Memory: Verbal and Non-Verbal Memorization Task	Stim decreased memory recall RT ~6% compared to sham (~990 ms vs ~1050 ms)	Approx 60 ms RT

Utilizing tDCS to mimic pre-REM oscillatory patterns during sleep, these researchers were able to enhance declarative memory consolidation. Although not yet replicated, this study demonstrates that neural oscillatory pattern mimicking is not only feasible but also seemingly efficacious.

11.4.6 Savant Skills: 'Global Neuroenhancement'

Table 11.6 summarizes two interesting cases of enhancement focusing of overall, 'global' capacities, and creativity. Snyder et al. (2003, 2006) have twice used TMS to induce so-called "savant skills" in healthy subjects. As defined by Snyder, savants are "rare individuals who, although severely brain impaired, display islands of astonishing excellence in specific areas including drawing, memory, music, calendar calculations, and arithmetic". Rather than ascribing to the repetitive practice or enhanced learning capability theories, Snyder advances the theory that savantism arises from paradoxical network facilitation (zero-sum) engendered by impaired function of the fronto-temporal lobes. More explicitly, Snyder believes the heavily networked frontal lobes are responsible for sending inhibitory signals to various neural regions, including those responsible for language production and processing, mathematical processing, and emotional processing. Accordingly, impaired function of the frontal lobes would diminish the number of inhibitory signals sent out thereby generating increased functionality of these correlated areas.

To test this hypothesis, Snyder utilized suppressive TMS over the left fronto-temporal lobe in a bid to paradoxically facilitate the functional networks within which the frontal lobes serve as inhibitory mediators. Although not present in every subject, impressive enhancements in mathematical and proofreading were reported for several subjects. In addition, artistic "scheme" shifts were reported for several subjects, suggesting both visual and mental object representations were affected by this protocol.

These findings are certainly exciting; however, they have gone largely unreplicated in the literature. Conclusive and reliable enhancement of this type will require additional, carefully controlled trials with larger numbers of subjects and objectively quantitative measurements of effect. In addition, as these studies rely on baseline comparison, future studies should remain cognizant of test–retest bias and employ a mixed condition design.

11.4.7 Considerations

When reviewing the above tables, one cannot help but feel a sense of excitement. It appears EM stimulation may indeed offer enhancement effects that could increase productivity, bolster performance, and better the lives of healthy

Table 11.6 EM savant-skill enhancement studies

Study	(n)	Region/s stimulated	Protocol	Cognitive domain / Task	Results	Enhancement
TMS						
Snyder et al. (2003)	11	Left Fronto-Temporal Lobe	0.5–1 Hz 15 min 90% rMT Offline	Savant Abilities: Drawing and Proofreading tasks	4 subjects adjusted shifted drawing schemes/ conventions. 2 subjects increased number of detected proofreading errors ~200% compared to baseline (~3 errors detected vs ~1 error detected)	Approx 2 word errors (out of 4)
Snyder et al. (2006)	12	Left Fronto-Temporal Lobe	1 Hz 15 min 90% rMT Offline	Savant Abilities: Discreet Object Estimation Task	Stim increased number of correct numerical–total guesses ~66% compared to sham (~5 correct vs ~3 correct)	Approx 2 correct guesses (out of 20)

individuals. However, before fantasy overshadows reality, there are several issues that must be addressed regarding the cited studies.

Small n. There is possibly nothing more difficult than recruiting healthy subjects for an unproven EM enhancement protocol. Accordingly, the *n* for many studies is rather small. Whereas it is true that small groups can yield large results, it is always prudent to remain cautious when extrapolating statistics to real-world populations.

Young Participants. As many of the above studies were conducted in a university setting, the majority of subjects were relatively young. Because it is well known that the neural networks change with advancing age (for a review, see Pascual-Leone et al. 2011), questions regarding the enhancement effects of EM devices on older and elderly subjects still remain largely (if not completely) unanswered. For instance, Reuter-Lorenz et al. (2000) utilized PET to demonstrate younger subjects display left-lateralized frontal activation during a WM task while older adults display bi-lateral frontal activation. This differential recruitment suggests that either right DLPFC inhibitory mechanisms sent by the left DLPFC fall apart in older adults or that a network connection between the two regions arises only with advancing age. Whichever supposition is true, utilizing an excitatory WM enhancement paradigm (as outlined above) may generate a bi-lateral over-activation in older adults thereby generating no or detrimental WM effects. Furthermore, it is also important to remember that the effects of EM stimulation may be different in older populations due to the impact of differences in scalp-brain distance, atrophy, shifts in effective connectivity, etc.

Small Effects. The majority of enhancement effects outlined above concern RTs, and many fall within the 30–70 ms range. Whereas 50 ms may be a large quantity during expedient RT tasks, it is difficult to qualify this effect outside the laboratory. In fact, when considering activities of daily living it is difficult to envision a scenario where 50 ms would constitute a relevant "enhancement".

Baseline versus Sham. Several studies determine enhancement effects by comparing post stimulation results to baseline measurements (as opposed to sham measurements). Whereas this is a perfectly valid measurement, it can sometimes be misleading. For example, even well designed studies can seem to generate internal contradictions, such as when baseline and sham measurements provide seemingly inconsistent data. These situations are challenging and, accordingly, it is important to note which comparative values researchers utilize and the justifications behind said decision.

Zero-Sum Detriment. If, as seems to be the case, many enhancement effects depend upon zero-sum shifting of network specific processing power, there will undoubtedly be secondary behavioral detriments. Although no concomitant detriments were reported in the above studies, it is important to note no detriments were explicitly sought out. If it comes to pass that enhancement can only come with detriment, cost-benefit questions become infinitely more difficult to answer.

Publication Bias. It is a sad but true fact that many unsuccessful or no-effect experiments are simply left out of the published literature. Accordingly, there is little to no data regarding failed trials or replication attempts. Without this data, it is difficult to conclude if many enhancements are simply one–off occurrences or representative of larger potentials.

11.4.8 Final Thoughts

EM neuroenhancement is certainly an exciting prospect. However, the field is nascent and, accordingly, the research is rather sparse. Although the conceptual mechanisms for enhancement appear to be feasible under a number of circumstances, whether or not the resultant effects would be *useful* in any typical, real-world setting remains unclear. For instance, although many studies have reported shortened RTs during performance tasks following stimulation, rarely is RT the cognitive aspect people are interested in enhancing. Future researchers might do well to select assessment tasks with a strong focus on modality-specific features: such as capacity when examining WM or comprehension when examining language. Additionally, as many measurements of enhancement may appear with concurrent detriments, a thorough review of targeted network connections and dynamics should be made prior to experimentation and relevant tasks should be utilized in an attempt to systematically explore said potential detriments. Finally, it is essential that future results be reported in detail, including raw numerical data. Although transformative statistics are helpful in determining significance, they leave open many questions regarding actual effect and effect sizes. We certainly feel there is ample evidence to warrant further exploration in this field, and by utilizing focused, between-subject, randomized, placebo-controlled designs, we feel we can begin to better elucidate EM stimulation effects in order to leverage network dynamics for healthy performance enhancement.

References

Achermann P, Borbely AA (1998) Temporal evolution of coherence and power in the human sleep electroencephalogram. J Sleep Res 7(Supp1):36–41

Andoh J, Artiges E, Pallier C, Riviere D, Mangin JF, Cachia A, Plaze M, Paillere-Martinot ML, Martinot JL (2006) Modulation of language areas with functional MR image-guided magnetic stimulation. Neuroimage 29(2):619–627

Andoh J, Artiges E, Pallier C, Riviere D, Mangin JF, Paillere-Martinot ML, martinet JL (2008) Priming frequencies of transcranial magnetic stimulation over Wernicke's area modulate word detection. Cerebral Cortex 18:210–216

Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB (2011) Improving working memory: the effect of combined cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul 4:84–89

Antal A, Nitsche MA, Kincses TZ, Kruse W, Hoffmann KP, Paulus W (2004a) Facilitation of visuo-motor learning by transcranial direct current stimulation of the motor and extrastriate visual areas in humans. Eur J Neurosci 19:2888–2892

Antal A, Nitsche MA, Kruse W, Kincses TZ, Hoffmann KP, Paulus W (2004b) Direct current sitmulation over V5 enhances visuomotor coordination by improving motion perception in humans. J Cognit Neurosci 164:521–527

Bashir S, Edwards D, Pascual-Leone A (2011) Neuronavigation increases the physiologic and behavioral effects of low-frequency rTMS of primary motor cortex in healthy subjects. Brain Topogr 24:54–64

Bogacz R, Hu PT, Holmes PJ, Cohen JD (2010) Do humans produce the speed-accuracy trade-off that maximizes reward rate? Q J Exp Psychol 63(5):863–891

Boggio PS, Castro LO, Savagim EA, Braite R, Cruz VC, Rocha RR, Rigonatti SP, Silva MTA, Fregni F (2006) Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. Neurosci Lett 404:232–236

Boggio PS, Fregni F, Valasek C, Ellwood S, Chi R, Gallate J, Pascual-Leone A, Snyder A (2009) Temporal lobe cortical electrical stimulation during the encoding and retrieval phase reduces false memories. PLoS One 4(3):e4959

Boroojerdi B, Phipps M, Kopylev L, Wharton CM, Cohen LG, Grafman J (2001) Enhancing analogic reasoning with rTMS over the left prefrontal cortex. Neurology 56(4):526–528

Boyd LA, Linsdell MA (2009) Excitatory repetitive transcranial magnetic stimulation to the left dorsal premotor cortex enhances motor consolidation of new skills. BMC Neurosci 10:72

Broadbent HJ, van den Eynde F, Guillaume S, Hanif EL, Stahl D, David AS, Campbell IC, Schmidt U (2011) Blinding success of rTMS applied to the dorsolateral prefrontal cortex in randomized sham-controlled trials: a systematic review. World J Biol Psychiatry 12(4):240–248

Buetefisch CM, Hines B, Shuster L, Pergami P, Mathes A (2011) Motor demand-dependent improvement in accuracy following low-frequency transcranial magnetic stimulation of left motor cortex. J Neurophysiol 106:1614–1621

Bullard LM, Browning ES, Clark VP, Coffman BA, Garcia CM, Jung RE, van der Merwe AJ, Paulson KM, Vakhtin AA, Wootton CL, Weisend MP (2011) Transcranial direct current stimulation's effect on novice versus experienced learning. Exp Brain Res 213:9–14

Cappa SF, Sandrini M, Rossini PM, Sosta K, Miniussi C (2002) The role of the left frontal lobe in action naming. Neurology 59:720–723

Catani M, Jones DK, Ffytche DH (2005) Perisylvian language networks of the brain. Ann Neurol 57(1):8–16

Cattaneo Z, Pisoni A, Papagno C (2011) Transcranial direct current stimulation over Broca's region improves phonemic and semantic fluency in healthy individuals. Neuroscience 183:64–70

Cerruti C, Schlaug G (2008) Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. J Cognit Neurosci 21(10):1980–1987

Chatterjee A (2004) Cosmetic neurology and cosmetic surgery: parallels, predictions, and challenges. Camb Q Healthc Ethics 16(2):129–137

Chatterjee A (2007) Cosmetic neurology: the controversy over enhancing movement, mentation, and mood. Neurology 63(6):968–974

Chen R, Cohen LG, Hallett M (1997) Role of the ipsilateral motor cortex in voluntary movement. Can J Neurol Sci 24(4):284–291

Chi R, Fregni F, Snyder AW (2010) Visual memory improved by non-invasive brain stimulation. Brain Res 1353:168–175

Cincotta M, Giovannelli F, Borgheresi A, Balestrieri F, Zaccara G, Inghilleri M, Berardelli A (2006) Modulatory effects of high-frequency repetitive transcranial magnetic stimulation on the ipsilateral silent period. Exp Brain Res 171(4):490–496

Clark VP, Coffman BA, Mayer AR, Weisend MP, Lane TDR, Calhoun VD, Raybourne EM, Garcia CM, Wassermann EM (2010). tDCS guided using fMRI significantly accelerates learning to identify concealed objects. NeuroImage, [Epub ahead of print]

Cogiamanian F, Marceglia S, Ardolino G, Barbieri S, Priori A (2007) Improved isometric force endurance after transcranial direct current stimulation over the human motor cortical areas. Eur J Neurosci 26:242–249

Cotelli M, Manenti R, Rosini S, Calabria M, Brambilla M, Bisiacchi PS, Zanetti O, Miniussi C (2010) Action and object naming in physiological aging: an rTMS study. Frontiers Aging Neurosci 2:151

Dafotakis M, Grefkes C, Wang L, Fink GR, Nowak DA (2008) The effects of 1 Hz rTMS over the hand area of M1 on movement kinematics of the ipsilateral hand. J Neural Transm 115:1269–1274

Day BL, Rothwell JC, Thompson PD, Maertens de Noordhout A, Nakashima K, Shannon K, Marsden CD (1989). Delay in the execution of voluntary movement by electrical or magnetic brain stimulation in intact man. Evidence for the storage of motor programs in the brain. Brain 112(3):649–663

De Vries MH, Barth AC, Maiworm S, Knecht S, Zwitserlood P, Floel A (2009) Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. J Cognit Neurosci 22(11):2427–2436

Dees RH (2007) Better brains, better selves? The ethics of neruoenhancements. Kennedy Inst Ethics J 17(4):371–395

Diekelmann S, Born J (2010) The memory function of sleep. Nat Rev Neurosci 11:114–126

Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C (2009) Enhancement of planning ability by transcranial direct current stimulation. J Neurosci 29(22):7271–7277

Drager B, Breitenstein C, Helmke U, Kamping S, Knecht S (2004) Specific and non-specific effects of transcranial magnetic stimulation on picture-word verification. Eur J Neurosci 20:1681–1687

Duann JR, Ide JS, Luo X, Li CS (2009) Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. J Neurosci 29(32):10171–10179

Duncan J, Owen AM (2000) Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci 23(10):475–483

Dutilh G, Wagenmakers EJ, Visser I, van der Maas HL (2011) A phase transition model for the speed-accuracy trade-off in response time experiments. Cognitive Sci 35(2):211–250

Eastman P (2007) The ethics of neuroenhancement: where should the line be drawn? Neurol Today 7(14):21–22

Farah MJ, Illes J, Cook-Deegan R, Gardner H, Kandal E, King P, Parens E, Sahakian B, Wolpe PR (2004) Neurocognitive enhancement: what can we do and what should we do? Nat Rev Neurosci 5(5):421–425

Fecteau S, Knoch D, Fregni F, Sultani N, Boggio P, Pascual-Leone A (2007) Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. J Neurosci 27(46):12500–12505

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibtition of the human motor cortex. J Physiol 453:525–546

Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C (2010) Namining facilitation induced by transcranial direct current stimulation. Behav Brain Res 208:311–318

Ferrucci R, Marceglia S, Vergari M, Cogiamanian F, Mrakic-Sposta S, Mameli F, Zago S, Barbieri S, Priori A (2008) Cerebellar transcranial direct current stimulation impairs the practice dependent proficiency increase in working memory. J Cognit Neurosci 20(9): 1687–1697

Floel A, Rosser N, Michka O, Knecht S, Breitenstein C (2008) Noninvasive brain stimulation improves language learning. J Cognit Neurosci 20(8):1415–1422

Floel A, Suttorp W, Kohl O, Kurten J, Lohmann H, Breitenstein C, Knecht S (2011). Non-invasive brain stimulation improves object-location learning in the elderly. Neurobiol Aging, [Epub ahead of print]

Forstmann BU, Dutilh G, Brown S, Neumann J, von Cramon DY, Riddeinkhof KR, Wagenmakers EJ (2008) Striatum and pre-SMA facilitate decision-making under time pressure. Proc Nat Acad Sci USA 105(45):17538–17542

Fox D (2011) Brain buzz. Nature 472:156–158

Fox MD, Halko M, Eldaief M, Pascual-Leone A (2012). Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). Neuroimage 62:2232–2243

Fregni F, Boggio PS, nitsche M, Bermpohl F, Antal A, Feredoes E, Marcolin MA, Rigonatti SP, Silva MTA, Paulus W, Pascual-Leone A (2005). Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 166:23–30

Gagnon G, Schneider C, Grondin S, Blanchet S (2011) Enhancement of episodic memory in young and healthy adults: a paired-pulse TMS study on encoding and retrieval performance. Neurosci Lett 488:138–142

Galea JM, Albert NB, Ditye T, Miall RC (2009) Disruption of the dorolateral prefrontal cortex facilitates the consolidation of procedural skills. J Cognit Neurosci 22(6):1158–1164

Gallate J, Chi R, Ellwood S, Snyder A (2009) Reducing false memories by magnetic pulse stimulation. Neurosci Lett 449:151–154

Gammaitoni L, Hanggi P, Jung P, Marchesoni F (1998) Stochastic resonance. Rev Mod Phys 70(1):223–287

Gregori B, Curra A, Dinapoli L, Bologna M, Accornero N, Berardelli A (2005) The timing and intensity of transcranial magnetic stimulation, and the scalp site stimulated, as variables influencing motor sequence performance in healthy subjects. Exp Brain Res 166:43–55

Hamidi M, Tononi G, Postle BR (2008) Evaluating frontal and parietal contributions to spatial working memory with repetitive transcranial magnetic stimulation. Brain Res 1230:202–210

Hamzelou J (2011) Natural brain state is primed to learn. New Sci 2826

Hanajima R, Ugawa Y, Machii K, Mochizuki H, Terao Y, Enomoto H, Furubayashi T, Shiio Y, Uesugi H, Kanazawa I (2001) Interhemispheric facilitation of the hand motor area in humans. J Physiol 531(Pt3):849–859

Hannula H, Neuvonen T, Savolainen P, Hiltunen J, Ma YY, Antila H, Salonen O, Carlson S, Pertovaara A (2010) Increasing top-down suppression from pre-frontal cortex facilitates tactile working memory. NeuroImage 49:1091–1098

Harpaz Y, Levkovitz Y, Lavidor M (2009) Lexical ambiguity resolution in Wernicke's area and its right homologue. Cortex 45:1097–1103

Hilgetag CC, Theoret H, Pascual-Leone A (2001) Enhanced visual spatial attention ipsilateral to rTMS-induced virtual lesions of human parietal cortex. Nat Neurosci 4(9):953–957

Holland R, Leff AP, Josephs O, Galea JM, Desikan M, Price CJ, Rothwell JC, Crinion J (2011) Speech facilitation by left inferior frontal cortex stimulation. Curr Biol 21:1–5

How Does the Brain Work? NOVA (2011) Science now PBS

Hsu TY, Tseng LY, Yu JX, Kuo WJ, Hung DL, Tzeng OJL, Walsh V, Muggleton NG, Juan CH (2011) Modulating inhibitory control with direct current stimulation of the superior medial frontal cortex. NeuroImage 56:2249–2257

Hummel FC, Heise K, Celnik P, Floel A, Gerloff C, Cohen LG (2010) Facilitating skilled right hand motor function in older subjects by anodal polarization over the left primary motor cortex. Neurobiol Aging 31:2160–2168

Hwang JH, Kim SH, Park CS, Bang SA, Kim SE (2010) Acute high-frequency rTMS of the left dorsolateral prefrontal cortex and attentional control in healthy young men. Brain Res 1329:152–158

Ivanoff J, Branning P, Marois R (2008) fMRI evidence for a dual process account of the speed-accuracy tradeoff in decision making. PLoS One 3(7):e2635

Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM (2005) Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 64:872–875

Jacobson L, Javitt DC, Lavidor M (2011) Activation of inhibition: diminishing impulsive behavior by direct current stimulation over the inferior frontal gyrus. J Cognit Neurosci 23(11):3380–3387

Jin Y, Phillips B, Pascual-Leone A, Leuchter AF (*In Press*). A method for treatment of major depression using EEG-based synchronized transcranial magnetic stimulation. IEEE

Kadosh RC, Soskic S, Iuculano T, Kanai R, Walsh VM (2010) Modulating neuronal activity produces specific and long-lasting changes in numerical competence. Curr Biol 20:2016–2020

Kang EK, Paik NJ (2011) Effect of a tDCS electrode montage on implicit motor sequence learning in healthy subject. Exp Trans Stroke Med 3(4):1–6

Kapur N (2011) The Paradoxical Brain. Cambridge University Press, London

Kim YH, Park JW, Ko MH, Jang SH, Lee PK (2004) Facilitative effects of high frequency subthreshold repetitive transcranial magnetic stimulation on complex sequential motor learning in humans. Neurosci Lett 367:181–185

Kincses TZ, Antal A, Nitsche MA, Bartfai O, Paulus W (2003) Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. Neuropsychologia 42:113–117

Kinsbourne M (2003) The corpus callosum equilibrates the cerebral hemispheres. In: Zaidel E, Iacoboni M (eds) The Parallel Brain. MIT Press, Cambridge

Kirschen MP, Davis-Ratner MS, Jerde TE, Schraedley-Desmond P, Desmond JE (2006) Enhancement of phonological memory following transcranial magnetic stimulation (TMS). Behav Neurol 17:187–194

Kobayashi M, Hutchinson S, Theoret H, Schlaug G, Pascual-Leone A (2004) Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. Neurology 62:91–98

Kobayashi M, Theoret H, Pascual-Leone A (2009) Suppression of ipsilateral motor cortex facilitates motor skill learning. Eur J Neurosci 29:833–836

Kohler S, Paus T, Buckner RL, Milner B (2004) Effects of left inferior prefrontal stimulation on episodic memory formation: a two-stage fMRI-rTMS study. J Cognit Neurosci 16(2):178–188

Kortmann R, Postma E, van der Kerik J (1999) Evolution of visual resolution constrained by a trade-off. Artificial Life 7(2):125–145

Luber B, Kinnunen LH, Rakitin BC, Ellsasser R, Stern Y, Lisanby SH (2007) Facilitation of performance in a working memory task with rTMS stimulation of the precuneus: frequency- and time-dependent effects. Brain Res 1128:120–129

Marshall L, Molle M, Born J (2003) Spindle and slow wave rhythms at slow wave sleep transitions are linked to strong shifts in the cortical direct current potential. Neuroscience 121(4):1047–1053

Marshall L, Molle M, Hallschmid M, Born J (2004) Transcranial direct current stimulation during sleep improves declarative memory. J Neurosci 24(44):9985–9992

Marshall L, Kirov R, Brade J, Molle M, Born J (2011) Transcranial electric currents to probe EEG brain rhythms and memory consolidation during sleep in humans. PLoS One 6(2):e16905

Matsuo A, Maeoka H, Hiyamizu M, Shomoto K, Morioka S, Seki K (2011) Enhancement of precise hand movement by transcranial direct current stimulation. NeuroReport 22:78–82

Merabet L, Pascual-Leone A (2010) Studies of crossmodal functions with TMS. In: Wassermann E et al (eds) Oxford handbook of transcranial magnetic stimulation. Oxford University Press, London

Molinuevo JL, Valls-Sole J, Valldeoriola F (2000) The effect of transcranial magnetic stimulation on reaction time in progressive supranuclear palsy. Clin Neurophysiol 111(11):2008–2013

Mottaghy FM, Hungs M, Brugmann M, Sparing R, Boroojerdi B, Foltys H, Huber W, Topper R (1999) Facilitation of picture naming after repetitive transcranial magnetic stimulation. Neurology 53(8):1806–1811

Mottaghy FM, Sparing R, Topper R (2006) Enhancing picture naming with transcranial magnetic stimulation. Behav Neurol 17:177–186

Mulquiney PG, Hoy KE, Daskalakis ZJ, Fitzgerald PB (2011). Improving working memory: exploring the effects of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. Clinical Neurophysiol [Epub ahead of print]

Najib U, Pascual-Leone A (2011) Paradoxical functional facilitation with noninvasive brain stimulation. In: Kapur N (ed) The paradoxical brain. Cambridge University Press, London

Nitsche MA, Schauenburg A, Lang N, Liebetanz D, Exner C, Paulus W, Tergau F (2003) Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. J Cognit Neurosci 15(4):619–626

Ohn SH, Park CI, Yoo WK, Ko MH, Choi KP, Kim GM, Lee YT, Kim YH (2008) Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Cogn Neurosci Neuropsychol 19(8):43–47

O'Reily JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H (2010) Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. Cereb Cortex 20:953–965

Pascual-Leone A, Gates JR, Dhuna A (1991) Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurology 41(5):697–702

Pascual-Leone A, Brasil-Neto JP, Valls-Sole J, Cohen LG, Hallett M (1992a) Simple reaction time to focal transcranial magnetic stimulation. Comparison with reaction time to acoustic, visual, and somatosensory stimuli. Brain 115(Pt1):109–122

Pascual-Leone A, Valls-Sole J, Wassermann EM, Brasil-neto J, Cohen LG, Hallett M (1992b) Effects of focal transcranial magnetic stimulation on simple reaction time to acoustic, visual, and somatosensory stimuli. Brain 115:1045–1059

Pascual-Leone A, Freitas C, Oberman L, Horvath JC, Halko M, Eldaief M, Bashir S, Vernet M, Shafi M, Westover B, Vahabzadeh-Hagh AM, Rotenberg A (2011) Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. Brain Topogr 24(3–4):302–315

Perez MA, Cohen LG (2009) The corticospinal system and transcranial magnetic stimulation in stroke. Top Stroke Rehabil 16(4):254–269

Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Noppeney U, Koepp MJ, Duncan JS (2006) Hemispheric asymmetries in language related pathways: a combined functional MRI and tractography study. Neuroimage 32(1):388–399

Preston G, Anderson E, Silva C, Goldberg T, Wassermann EM (2009) Effects of 10 Hz rTMS on the neural efficiency of working memory. J Cognit Neurosci 22(3):447–456

Reichenbach A, Whittingstall K, Thielscher A (2011) Effects of transcranial magnetic stimulation on visual evoked potentials in a visual suppression task. Neuroimage 54(2):1375–1384

Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, Celnik PA, Krakauer JW (2009) Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. PNAS 106(5):1590–1595

Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C, Koeppe RA (2000) Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cognit Neurosci 12(1):174–187

Rilling JK, Glasser MF, Preuss TM, Ma X, Zhao T, Hu X, Behrens TE (2008) The evolution of the arcuate fasciculus revealed with comparative DTI. Nat Neurosci 11(4):426–428

Ross LA, McCoy D, Wolk DA, Coslett HB, Olson IR (2010) Improved proper name recall by electrical stimulation of the anterior temporal lobes. Neuropsychologia 48:3671–3674

Sauseng P, Klimesch W, Heise KF, Gruber WR, Holz E, Karim AA, Glennon M, Gerloff C, Birbaumer N, Hummel FC (2009) Brain oscillatory substrates of visual short-term memory capacity. Curr Biol 19(21):1846–1852

Savolainen P, Carlson S, Boldt R, Neuvonen T, Hannula H, Hiltunen J, Salonen O, Ma YY, Pertovaara A (2011) Facilitation of tactile working memory by top-down suppression from prefrontal to primary somatosensory cortex during sensory interference. Behav Brain Res 219:387–390

Sawaki L, Okita T, Fujiwara M, Mizuno K (1999) Specific and non-specific effects of transcranial magnetic stimulation on simple and go/no-go reaction time. Exp Brain Res 127:402–408

Schutter DJLG, van Honk J (2006) Increased positive emotional memory after repetitive transcranial magnetic stimulation over the orbitofrontal cortex. J Psych Neurosci 31(2):101–104

Schwarzkopf DS, Silvanto J, Rees G (2011) Stochastic resonance effects reveal the neural mechanisms of transcranial magnetic stimulation. J Neurosci 31(9):3143–3147

Silvanto J, Pascual-Leone A (2008) State-dependency of transcranial magnetic stimulation. Brain Topogr 21(1):1–10

Silvanto J, Cattaneo Z (In Press). State-dependent TMS protocols. In: Rotenberg A, Horvath JC, Pascual-Leone A (eds) NeuroMethods: TMS. Springer Books, London

Smillie LD, Gokcen E (2010) Caffeine enhances working memory for extraverts. Biol Psychol 85(3):496–498

Snyder AW, Mulcahy E, Taylor JL, Mitchell DJ, Sachdev P, Gandevia SC (2003) Savant-like skills exposed in normal people by suppressing the left fronto-temporal lobe. J Integr Neurosci 2(2):149–158

Snyder A, Bahramali H, Hawker T, Mitchell DJ (2006) Savant-like numerosity skills revealed in normal people by magnetic pulses. Perception 35:837–845

Sparing R, Mottaghy FM, Hungs M, Brugmann M, Foltys H, Huber W, Topper R (2001) Repetitive transcranial magnetic stimulation effects on language function depend on the stimulation parameters. J Clin Neurophysiol 18(4):326–330

Sparing R, Dafotakis M, Meister IG, Thirugnanasambandam N, Fink GR (2008) Enhancing language performance with non-invasive brain stimulation: a transcranial direct current stimulation study in healthy humans. Neuropsychologia 46:261–268

Tanaka S, Hanakawa T, Honda M, Wanatabe K (2009) Enhancement of pinch force in the lower leg by anodal transcranial direct current stimulation. Exp Brain Res 196:459–465

Tecchio F, Zappasodi F, Assenze G, Tombini M, Vollaro S, Barbati G, Rossini PM (2010) Anodal transcranial direct current stimulation enhances procedural consolidation. J Neurophysiol 104:1134–1140

Teo JT, Swayne OB, Cheeran B, Greenwood RJ, Rothwell JC (2011) Human theta burst stimulation enhances subsequent motor learning and increases performance variability. Cereb Cortex 21:1627–1638

Terao Y, Ugawa Y, Suzuki M, Sakai K, Hanajima R, Gemba-Shimizu K, Kanazawa I (1997) Shortening of simple reaction time by peripheral electrical and submotor-threshold magnetic cortical stimulation. Exp Brain Res 115:541–545

Thut G, Pascual-Leone A (2010) Integrating TMS with EEG: how and what for? Brain Topogt 22(4): 215–218

Topper R, Mottaghy FM, Brugmann M, Noth J, Huber W (1998) Facilitation of picture naming by focal transcranial magnetic stimulation of Wernicke's area. Exp Brain Res 121:371–378

Valldeoriola F, Valls-Sole J, Tolosa E, Ventura PJ, Nobbe FA, Marti MJ (1998) Effects of a startling acoustic stimulus on reaction time in different parkinsonian syndromes. Neurology 51(5):1315–1320

Van Veen V, Krug MK, Carter CS (2008) The neural and computational basis of controlled speed-accuracy tradeoff during task performance. J Cognit Neurosci 20(11):1952–1965

Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, D'haenen H (2006a) The influence of rTMS over the right dorsolateral prefrontal cortex on intentional set switching. Exp Brain Res 172:561–565

Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, D'haenen H (2006b) The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. Exp Brain Res 169:279–282

Vanderhasselt MA, De Raedt R, Leyman L, Baeken C (2010) Role of the left DLPFC in endogenous task preparation: experimental transcranial magnetic stimulation study. Neuropsychobiology 61:162–168

Vines BW, Nair DG, Schlaug G (2007) Contralateral and ipsilateral motor effects after transcranial direct current stimulation. NeuroReport 17(6):671–674

Vines BW, Cerruti C, Schlaug G (2008) Dual-hemisphere tDCS facilitates improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation. BMC Neuroscience 9(103):1–7

Wagner T, Valero-Cabre A, Pascual-Leone A (2007) Noninvasive human brain stimulation. Annu Rev Biomed Eng 9:527–565

Williams JA, Pascual-Leone A, Fregni F (2010) Interhemispheric modulation induced by cortical stimulation and motor training. Phys Ther 90(3):398–410

Yamanaka K, Yamagata B, Tomioka H, Kawasaki S, Mimura M (2010) Transcranial magnetic stimulation of the parietal cortex facilitates spatial working memory: near-infrared spectroscopy study. Cereb Cortex 20:1037–1045

Yeshurun Y, Levy L (2003) Transient spatial attention degrades temporal resolution. Psychol Sci 14(3):225–231

Zaehle T, Sandmann P, Thorne JD, Jancke L, Herrmann CS (2011) Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neuroscience 12:2

Part III
Changes in Connectivity and Functions in Diseases

Chapter 12
Changes in Cortical Circuits in Movement Disorders

Zhen Ni and Robert Chen

Abstract Transcranial magnetic stimulation (TMS) can be used to investigate the intracortical circuits within the primary motor cortex (M1) and connections from other cortical areas to the M1. Repetitive TMS (rTMS) is able to modify the cortical excitability and can be used to test the cortical plasticity. In Parkinson's disease (PD), there are impairments in intracortical circuits, indicating abnormal modulation of M1 excitability by intrahemispheric and interhemispheric inputs. Organic and psychogenic dystonia may have similar impairment in intracortical circuits but may have differences in cortical plasticity. Essential tremor and PD tremor respond differently to a resetting stimulus applied to different sites along the pathway for tremor generation and transmission, suggesting that they have different pathophysiological origins. Intracortical circuits may be impaired in Tourette's syndrome but tend to normalize during task performance. Repeated applications of rTMS may induce long-term changes in cortical excitability. It is being developed as a potential treatment to normalize cortical excitability and intracortical circuits for movement disorders.

Abbreviations

AMT	Active motor threshold
CBI	Cerebellar inhibition
CMCT	Central motor conduction time
CS	Conditioning stimulus

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D-wave	Direct wave
DBS	Deep brain stimulation
EMG	Electromyogram
ET	Essential tremor
GABA	Gamma-aminobutyric acid
I-wave	Indirect wave
ICF	Intracortical facilitation
ISI	Interstimulus interval
LAI	Long latency afferent inhibition
LICI	Long interval intracortical inhibition
LIHI	Long latency interhemispheric inhibition
M1	Primary motor cortex
MEP	Motor evoked potential
PAS	Paired associative stimulation
PD	Parkinson's disease
RMT	Rest motor threshold
rTMS	Repetitive transcranial magnetic stimulation
SAI	Short latency afferent inhibition
SICF	Short interval intracortical facilitation
SICI	Short interval intracortical inhibition
SIHI	Short latency interhemispheric inhibition
SP	Silent period
TMS	Transcranial magnetic stimulation
TS	Test stimulus

12.1 Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive and painless method to stimulate the human brain (Barker et al. 1985). The current flow in the coil creates a magnetic field that is perpendicular to the coil and induces an electrical current in the underlying brain tissue parallel to the current flow in the coil. If stimulation is applied to the primary motor cortex (M1), it activates facilitatory interneurons and produces descending volleys in the corticospinal pathway. This in turn discharges spinal motoneurons and generates motor evoked potential (MEP) in the target muscles (Hallett 2007). In addition to activation of corticospinal neurons, TMS also activates intracortical inhibitory and excitatory neural circuits within or outside the M1. Repetitive TMS (rTMS) refers to application of trains of regularly repeating TMS pulses. These pulses temporally summate to cause greater changes in neural activity than a single-pulse. Such effects lead to the modulation on cortical excitation and inhibition that can outlast the stimulation by minutes to

hours (Wassermann 1998), which could be used as therapeutic tools in neurologic and psychiatric disorders. In this chapter, we will discuss the use of TMS in the investigation of cortical circuits in movement disorders and its potential therapeutic applications.

12.2 Parkinson's Disease

Parkinson's disease (PD) is associated with functional deficits in multiple brain areas. It has been hypothesized that deficient activation of the basal ganglia in PD patients leads to excessive beta-band oscillations and alters thalamocortical input to the M1. Many TMS studies have been performed to investigate the pathophysiologic mechanisms and to develop new therapies in PD.

12.2.1 Motor Evoked Potential

12.2.1.1 MEP Latency

MEP latency refers to the time from TMS delivery to MEP onset. Central motor conduction time (CMCT) is the conduction time from the M1 to the motoneuron pool in the spinal cord or brainstem. CMCT can be measured with TMS by substracting the peripheral conduction time from the MEP latency. The peripheral conduction time can be obtained by spinal stimulation or F-wave measurement (Chen et al. 2008). MEP latency and CMCT are normal in PD, suggesting that the conductions in the cortex and along the corticospinal axon are not affected by the disease. However, patients with multiple system atrophy may show abnormal lengthening in CMCT, which may be useful for establishing the diagnosis (Abbruzzese et al. 1997). In addition, patients with autosomal recessive *parkin* show longer CMCT than healthy controls while asymptomatic carriers do not show such abnormality (Schneider et al. 2008). It should be noted that shortened MEP latency in PD has been reported. The results should be interpreted cautiously because tremor and rigidity are common in PD and they can cause background electromyographic (EMG) activities which may shorten the rest MEP latency by several milliseconds (Rothwell 1997).

12.2.1.2 Motor Threshold

Motor threshold is an important parameter of motor cortical excitability. Rest and active motor thresholds (RMT and AMT) are defined as the minimum TMS intensities that elicit small but reproducible MEPs at rest and during voluntary muscle contraction, respectively (Rossini et al. 1994). The motor threshold reflects

the excitability of the most sensitive group of neurons in the stimulated area in M1. Most studies have reported that RMT is normal in PD. Involuntary contraction caused by tremor and rigidity may also contaminate the measurement of RMT in PD. In PD patients with rigidity, Cantello et al. (1991) showed that RMT was lower on the more affected side compared to the less affected side and to healthy controls, but most studies reported no change in RMT in PD (Chen et al. 2008). AMT in PD appears to be normal although correlation between the degree of bradykinesia and AMT has been reported (Ellaway et al. 1995). In addition, AMT does not change with the levodopa (Ridding et al. 1995a) or deep brain stimulation (DBS) of the internal globus pallidus (Chen et al. 2001) or the subthalamic nucleus (Cunic et al. 2002).

12.2.1.3 MEP Amplitude and Recruitment Curve

MEP amplitude reflects the global excitability of cortical excitatory and inhibitory interneurons, large corticospinal neurons, and spinal motoneurons. Recruitment curve, also referred to as input–output curve, depicts the rise of MEP size with increasing TMS intensities. The curve is usually sigmoid shaped and slope of the curve reflects the strength of corticospinal projections in the target muscle (Chen et al. 1998). Increased MEP amplitude and recruitment curve at rest in PD patients has been reported in some studies (Cantello et al. 1991; Valls-Sole et al. 1994). Patients with internal globus pallidus DBS also showed larger MEP amplitude than controls whether the DBS was turned on or off (Chen et al. 2001). This increased MEP amplitude in PD may suggest that there is an imbalance toward disinhibition in the motor pathway that may include both cortical and spinal motoneurons. This is consistent with the observation that spinal motoneurons in PD are hyperexcitable as shown by increased amplitudes of F-waves and H-reflexes compared to healthy controls (Sax et al. 1977; Valls-Sole et al. 1994). On the other hand, enhancement in MEP amplitude and recruitment curve caused by muscle contraction may be less significant in PD patients than that in controls, and this may be related to increased motor excitability in PD at rest condition (Valls-Sole et al. 1994).

12.2.2 Silent Period

When TMS is applied during voluntary contraction, a silent period (SP) can be recorded in the ongoing EMG following the MEP. The first part of the SP is partly due to decreased spinal excitability that involves motoneuronal refractoriness and Renshaw inhibition. The latter part of the SP mainly involves inhibitory effects at the cortical level, mediated by gamma-aminobutyric acid type B ($GABA_B$) receptors (Siebner et al. 1998; Werhahn et al. 1999). Shortening in SP in PD (Cantello et al. 2002) has been confirmed by many studies. However, such

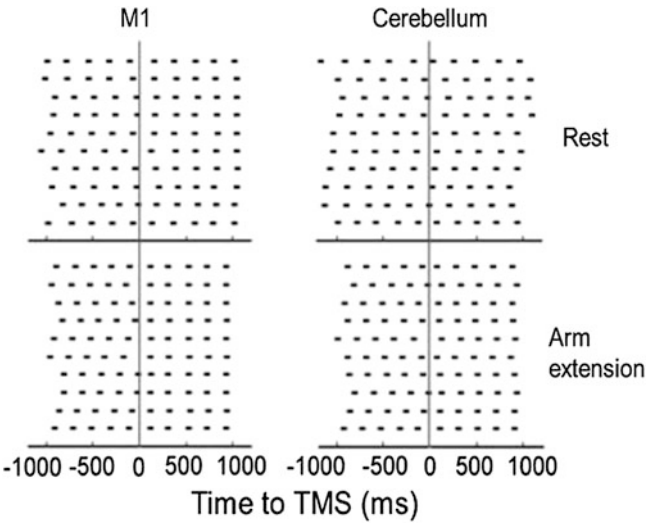
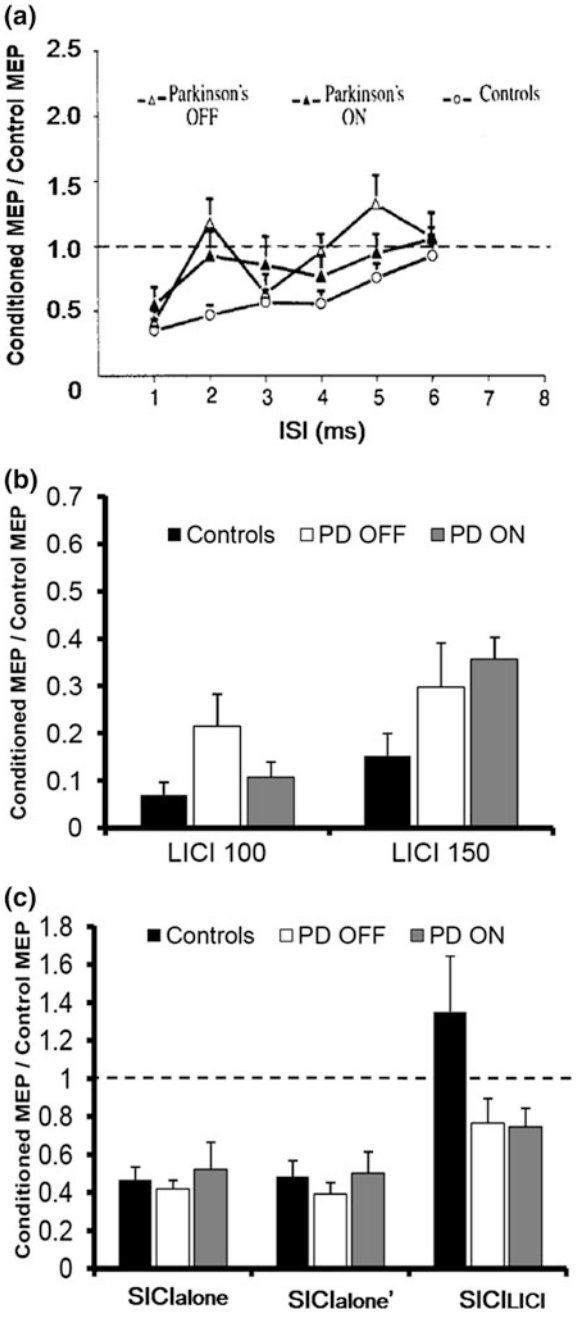


Fig. 12.1 Tremor reset in Parkinson's disease. Raster plots of five tremor bursts preceding and following the stimulations are shown. Tremor bursts were recorded from the flexor carpi radialis muscle in a Parkinson's disease patient with surface EMG. Each row represents a single trial. The *vertical lines* (time 0) represent the time of TMS. Note that, the tremor bursts before TMS were not related to the time of TMS delivery. After M1 TMS in both rest and arm extension conditions (*left panels*), tremor bursts were time-locked to TMS. For cerebellar stimulation with arm at rest (*right upper panel*), the tremor bursts after TMS were not time-locked but they were time-locked with arms extended (*right lower panel*). *M1* primary motor cortex; *TMS* transcranial magnetic stimulation. Modified from Ni et al. (2010)

abnormality in PD may not be pronounced at low stimulus intensities (Ridding et al. 1995a). Dopaminergic medication normalizes the shortened SP in PD (Priori et al. 1994; Ridding et al. 1995a). High doses of levodopa may even lengthen the SP duration beyond the normal range (Chen et al. 2001).

12.2.3 Tremor Reset

An asymmetric 4–6 Hz resting tremor is a cardinal symptom of PD (Lang and Lozano 1998). Many PD patients also have postural tremor that may be more prominent and disabling than rest tremor, and may be the first manifestation of the disease (Jankovic et al. 1999). When stimulation is applied to the motor pathway, the tremor may be transiently disrupted. The reoccurrence of the tremor is then time-locked to the stimulation and this phenomenon is referred to as tremor reset (Fig. 12.1). Tremor reset can be used to assess whether the stimulated brain area is involved in the generation or transmission of tremor (Pascual-Leone et al. 1994). A previous study showed that mechanical perturbation which modulates spinal reflex pathways has very little effect on postural tremor in PD, suggesting that spinal circuits may not be involved in generating PD postural tremor (Lee and Stein 1981).


(a)
Conditioned MEP / Control MEP
2.5
2.0
1.5
1.0
0.5
0
Parkinson's OFF
Parkinson's ON
Controls
1
2
3
4
5
6
7
8
ISI (ms)
(b)
Conditioned MEP / Control MEP
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Controls
PD OFF
PD ON
LICI 100
LICI 150
(c)
Conditioned MEP / Control MEP
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Controls
PD OFF
PD ON
SICIalone
SICIalone'
SICILICI

◀**Fig. 12.2** Short and long interval intracortical inhibitions in Parkinson's disease. The conditioned MEP amplitudes were expressed as a ratio to the MEP amplitude of test stimulus alone (control). Values below 1 indicate inhibition and those above 1 indicate facilitation. **a** SICI tested in 11 PD patients and 10 healthy controls. SICI was decreased in PD patients in the off medication state. The decreased SICI was partly normalized in the on medication state. **b** LICI at ISIs of 100 and 150 ms tested in 11 PD patients and 9 healthy controls. LICI at both ISIs was decreased in PD patients in both off and on medication states. **c** Interaction between SICI and LICI tested in 11 PD patients and 9 healthy controls. The ISI for testing SICI was 2 ms. ISI for testing LICI was 100 ms. $SICI_{alone}$ represents SICI with the test MEP of ~1 mV. $SICI_{alone}$, represents SICI with test stimulus intensity able to generate MEP of ~1 mV in the presence of LICI. $SICI_{LICI}$ represents SICI in the presence of LICI. Note that, $SICI_{LICI}$ was weaker than $SICI_{alone}$ and $SICI_{alone}$, in healthy controls. The reduction in SICI in the presence of LICI was absent in PD patients in both medication off and on states. *ISI* interstimulus interval; *LICI* long interval intracortical inhibition; *PD* Parkinson's disease; *SICI* short interval intracortical inhibition. Modified from Ridding et al. (1995a) and Chu et al. (2009)

Subsequent investigations found that TMS applied to M1 completely resets postural tremor in PD (Britton et al. 1993; Pascual-Leone et al. 1994). A recent study showed that PD rest tremor can also be reset by motor cortical TMS, suggesting that the M1 is involved in both resting and postural tremor in PD. In addition, cerebellar TMS is effective in resetting the PD postural tremor but not rest tremor (Fig. 12.1), suggesting that the cerebellum is involved in the generation or transmission of postural tremor but not rest tremor in PD (Ni et al. 2010). However, it is possible that stronger cerebellar stimulation could reset PD rest tremor (Hallett and Deuschl 2010).

12.2.4 Intracortical Circuits

The excitability of intracortical circuits can be investigated by a paired-pulse TMS paradigm. The effect of the first conditioning stimulus (CS) on the MEP elicited by the second test stimulus (TS) depends on the intensities of the stimuli, the interstimulus interval (ISI), and where the CS was applied. Using these paradigms, the intracortical circuits in PD have been extensively studied and the results have contributed to the current knowledge of the pathophysiologic mechanisms of PD.

12.2.4.1 Short and Long Interval Intracortical Inhibitions

Short interval intracortical inhibition (SICI) and facilitation (ICF) can be tested with both CS and TS delivered to the M1 through the same coil, with a subthreshold CS followed by a suprathreshold TS. The test MEP is inhibited at ISI of 1–5 ms, and facilitated at ISI of 7–30 ms (Kujirai et al. 1993). SICI is likely mediated by $GABA_A$ receptors. The mechanism mediating ICF remains unclear. The first study of SICI in PD showed that SICI is reduced in PD patients and levodopa partly normalizes this impaired inhibition (Ridding et al. 1995a) (Fig. 12.2a). DBS of the subthalamic nucleus increased the reduced SICI both in

the on and off medication states (Cunic et al. 2002; Dauper et al. 2002) while DBS of the internal globus pallidus has little effect on SICI (Chen et al. 2001). However, other studies reported that SICI was normal in PD patients either on or off medication (Chu et al. 2009) and decreased SICI was found only at high CS intensities (MacKinnon et al. 2005). These findings led to the argument that increased MEP amplitude detected in SICI measurement may be caused by increased facilitation rather than decreased inhibition. Since ICF is normal in PD patients (Ridding et al. 1995a), enhancement in other cortical facilitatory circuits such as short interval intracortical facilitation (SICF) may be considered especially since the stimulus parameters to elicit SICI and SICF partly overlap (Peurala et al. 2008).

Long interval intracortical inhibition (LICI) is elicited when a suprathreshold CS is applied 50–200 ms prior to the TS (Valls-Solé et al. 1992; Wassermann et al. 1996). LICI is likely mediated by $GABA_B$ receptors. Some studies found that LICI at ISIs of 100 and 150 ms is decreased in PD (Chu et al. 2009) (Fig. 12.2b), consistent with shortened SP ($GABA_B$ receptors mediated) in PD. However, other studies reported opposite results of increased LICI in PD and tendency to normalize with levodopa (Valzania et al. 1997), and another study showed normal LICI in both on and off mediation states in PD (Sailer et al. 2003). One possibility that leads to inconsistency in LICI in PD is that these studies used different stimulus parameters, including the CS intensity and ISI. In addition, observation of LICI in PD at rest (Chu et al. 2009) and under slight muscle contraction (Berardelli et al. 1996) may be different.

Using a triple-pulse TMS paradigm, it has been found that LICI inhibits SICI in a manner consistent with presynaptic inhibition (Sanger et al. 2001). The suppressive effect of LICI on SICI seen in healthy controls is absent in PD patients (Fig. 12.2c). Dopaminergic medications did not normalize this deficit. The results suggest that presynaptic inhibition is impaired in PD and the impairment may be a nondopaminergic feature of PD (Chu et al. 2009).

12.2.4.2 Interhemispheric Inhibition

Interhemispheric inhibition (IHI) can be measured by two coils placed on opposite M1s. Both CS and TS are suprathreshold. Short and long latency IHI (SIHI and LIHI) peak at ISIs of $\sim$10 and 50 ms. IHI is likely produced by interhemispheric inputs largely mediated through the corpus callosum (Ferbert et al. 1992; Ni et al. 2009). There is less LIHI in PD patients with mirror movement than those without mirror movement, suggesting that deficits in transcallosal function may contribute to mirror activity in PD. Such abnormality is found for LIHI from both the less affected to more affected side and vice versa. There is no significant abnormality in SIHI in PD patients (Li et al. 2007).

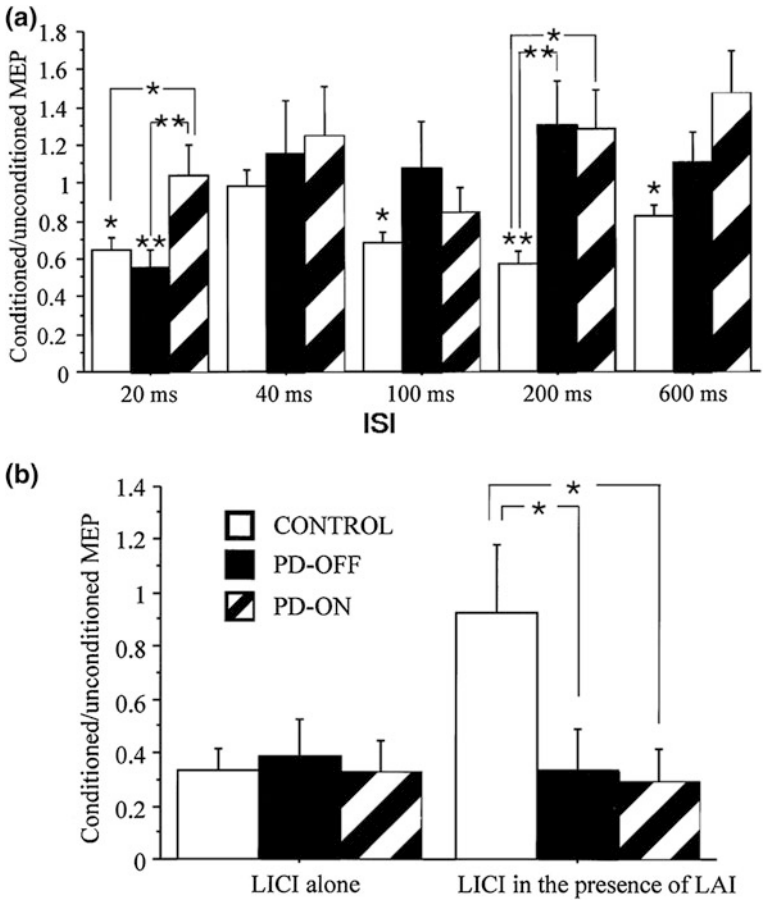


Fig. 12.3 Afferent inhibition in Parkinson's disease. The conditioned MEP amplitudes were expressed as a ratio to the MEP amplitude of the test stimulus alone (control). The value below 1 indicates inhibition and that above 1 indicates facilitation. Data obtained from 10 PD patients and 10 healthy controls. The white columns represent data from healthy controls. The black columns represent data from PD patients off medications and the hatched columns represent data from PD patients on mediations. **a** Afferent inhibition tested at different ISIs. Note that, SAI tested at ISI of 20 ms was comparable for PD off and controls. With medication on, SAI became weaker in PD patients. LAI tested at ISI of 200 ms was reduced in PD patients whether on or off medications. **b** LICI in the presence of LAI tested with a triple-pulse paradigm. ISI for LICI was 100 ms and that for LAI was 200 ms. LICI alone was similar for the PD on, off, and control groups. In the presence of LAI, LICI was reduced in healthy controls. Such modulation of LICI by LAI was absent in PD patients whether on or off medications. $*P < 0.05$, $**P < 0.01$, comparison between different groups. *ISI* interstimulus interval; *LAI* long latency afferent inhibition; *LICI* long interval intracortical inhibition; *PD* Parkinson's disease; *SAI* short latency afferent inhibition. Modified from Sailer et al. (2003)

12.2.4.3 Afferent Inhibition

Afferent input activated by electrical peripheral nerve stimulation inhibits the contralateral M1. Short (Tokimura et al. 2000) and long (Chen et al. 1999) latency afferent inhibition (SAI and LAI) refer to the inhibitory phases at ISIs of ~20 and ~200 ms. Cholinergic (Di Lazzaro et al. 2000) and GABA (Di Lazzaro et al. 2005) mediated pathways are involved in generating SAI, whereas transmitter involved in LAI is not known. A previous study showed that SAI is normal in PD off dopaminergic medications, but it is reduced on medication state (Fig. 12.3a). SAI probably represents a direct interaction between the sensory inputs and the M1. This pathway is unaffected by PD but is altered by dopaminergic medication and may contribute to the side effects of dopaminergic drugs. LAI is reduced in PD patients independent of their medication status. LAI probably involves indirect interactions between sensory inputs and the M1 via the basal ganglia or other cortical areas. This defective sensorimotor integration may be a nondopaminergic manifestation of PD (Sailer et al. 2003). In addition, reduced SAI in the on medication state in PD could be restored by subthalamic nucleus DBS and reduced LAI was partially normalized by DBS in the on medication state (Sailer et al. 2007).

The modulation of intracortical circuits by afferent inputs can also be tested with a triple-pulse TMS paradigm. While LICI is reduce in the presence of LAI in healthy subjects, such modulation of LICI by the afferent inputs is impaired in PD patients in both off and on medication states (Fig. 12.3b), which is manifested as similar degree of LICI in the presence of LAI compared to LICI alone (Sailer et al. 2003).

12.2.4.4 Cerebellar Inhibition

Cerebellar inhibition (CBI) refers to the phenomenon that stimulation over the cerebellum suppresses the response to subsequent stimulation of the contralateral M1. CBI is mediated by the cerebellothalamocortical pathway. Cerebellar TMS likely activates cerebellar Purkinje's cells that inhibit the deep cerebellar nuclei, which has an excitatory projection to the motor cortex via the ventral thalamus. Therefore, the net result of cerebellar stimulation is inhibition of the M1 5–7 ms later (Ugawa et al. 1995; Pinto and Chen 2001). CBI is decreased in PD patients. Moreover, decreased CBI correlated with the degree of reset of postural tremor caused by cerebellar stimulation, suggesting that the deficits on the cerebellothalamocortical pathway may be related to the generation or transmission of PD postural tremor (Ni et al. 2010). In addition, this cerebellar dysfunction in PD might be improved by dopaminergic mediation as CBI became normal in PD patients on medications (Shirota et al. 2010).

12.2.4.5 Connectivity Between the Basal Ganglia and the Primary Motor Cortex

Inputs from the basal ganglia modulate M1 excitability. In PD patients with subthalamic nucleus DBS, cortical evoked potential studies showed that subthalamic nucleus DBS led to potentials with peak latencies of about 3 and 20 ms (Ashby et al. 2001; Kuriakose et al. 2010). In order to investigate whether the evoked potentials are associated with changes in cortical excitability, studies with single-pulse subthalamic nucleus DBS followed by TMS to the M1 found two phases of cortical facilitation at ISIs of 2–4 ms and 21–24 ms. Therefore, the times of cortical facilitation coincide with latencies of cortical evoked potentials from subthalamic nucleus DBS. Antidromic stimulation of the corticosubthalamic pathway likely mediates the early phase of facilitation while the late phase is likely mediated by synaptic transmission through the basal ganglia-thalamo-cortical circuit (Kuriakose et al. 2010).

12.2.5 Cortical Plasticity in PD

Cortical plasticity can be tested by paired associative stimulation (PAS). PAS involves an electrical peripheral nerve stimulation followed by TMS to M1 applied repetitively. Heterosynaptic, spike-timing dependent plasticity is considered the most likely underlying mechanism for PAS. If median nerve stimulation precedes TMS by about 25 ms, the two stimuli arrive at the M1 at about the same time and lead to facilitation in M1 (Stefan et al. 2000). While PAS at ISI of $\sim$25 ms significantly increases MEP size in healthy subjects, such cortical plasticity is impaired in PD patients off medication. In addition, dopaminergic medications restored the potentiation of MEP amplitudes induced by PAS in the nondyskinetic PD patients but not in the dyskinetic PD patients (Morgante et al. 2006), suggesting that the development of dyskinesia is associated with disturbance of cortical plasticity.

On the other hand, plasticity at the postsynaptic terminal generated by homogenous inputs can be tested by rTMS. A recent study found increased MEP amplitude after intermittent theta burst stimulation in PD patients (Benninger et al. 2011), similar to the effects seen in healthy controls (Huang et al. 2005). A further study confirmed the increases in MEP amplitude over the course of 60 min in PD patients whether the medication status was on or off (Zamir et al. 2012). In addition, changes in intracortical circuits induced by intermittent theta burst stimulation were also similar for PD on, PD off, and healthy controls. These results suggests that spike-timing dependent heterosynaptic plasticity may be more impaired in PD than homosynaptic plasticity because PAS but not theta burst stimulation induced plasticity is impaired in PD patients. However, another study reported that theta burst stimulation applied to a group of PD patients with more severe symptoms did not produce MEP facilitation either with on or off medication

(Suppa et al. 2011). In addition, a short train of continuous theta burst stimulation followed by physical practice generated MEP facilitation in both PD patients without dyskinesia while on medication and in healthy controls. A second short train of theta burst stimulation following this facilitatory protocol produced depotentiation like effects which canceled the MEP increase in both subject groups. In PD patients with dyskinesia, the former facilitatory protocol produced similar MEP facilitation when the patients took half the dose of their usual medication. However, the later depotentiation protocol no longer had effect in the dyskinetic group. These result are consistent with the notion that the development of dyskinesia in PD patients is associated with impairment in motor cortical plasticity (Huang et al. 2011).

12.2.6 Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) involves trains of TMS pulses delivered with durations from hundreds of milliseconds to several minutes at various frequencies and intensities. The effects of the pulses temporally summate to cause a greater and longer duration changes in neural activity than a single-pulse. Since the effects of a single session of rTMS can last for several hours and repeated sessions may last for months, it is a potential treatment for many neurologic disorders, including PD. Generally, high-frequency rTMS potentiates MEP and low-frequency rTMS suppresses MEP when delivered to the M1 (Hallett 2007). High-frequency rTMS of the cortex leads to dopamine release in the basal ganglia both in healthy controls (Strafella et al. 2003) and PD patients (Strafella et al. 2006). While many studies investigated the effects of rTMS on PD symptoms, the results are variable (Edwards et al. 2008). A large placebo effect with sham stimulation has been observed (Okabe et al. 2003). A meta-analysis found that high-frequency rTMS improved motor symptoms in PD patients while low-frequency rTMS had little benefit (Elahi et al. 2009). In one study, improvement in motor symptoms after rTMS was found only when the patients were on medication, suggesting that dopaminergic medication may influence the effects of rTMS in PD (Buhmann et al. 2004). Since the previous rTMS studies in PD only involve a small number of patients and many of them are only of short duration, a large randomized, controlled trial is needed to establish the efficacy of high-frequency rTMS in the treatment of PD motor symptoms. In addition to regular rTMS, intermittent theta burst stimulation has also been used to treat PD motor symptoms. However, a study used eight sessions of intermittent theta burst stimulation over 2 weeks did not find long-term effect on PD symptoms but there was benefits on mood (Benninger et al. 2011).

Low-frequency rTMS has been used to treat levodopa induced dyskinesia. 1 Hz rTMS over the M1 with a 2-week course may produce short-term improvement in levodopa induced dyskinesia (Wagle-Shukla et al. 2007). Similar improvement was confirmed by a placebo-controlled study. However, significant improvement

in dyskinesia after rTMS was only found when compared to baseline and the difference between real and sham stimulations was not significant (Filipovic et al. 2009).

Stimulation of other areas outside the M1 may also be effective. In particular, a sham-controlled study with a relatively large sample size reported that 5 Hz rTMS applied to the supplymentary motor area significantly improved the clinic rating scores and bradykinesia in PD patients (Hamada et al. 2008). Continuous theta burst stimulation, a type of inhibitory rTMS, delivered to the cerebellum improved peak-dose levodopa induced dyskinesia in PD (Koch et al. 2009). While it was reported that a 5 Hz rTMS applied to M1 produced MEP facilitation in healthy controls but not in PD patients whether on or off medications, a conditioning train of 5 Hz rTMS delivered to dorsal premotor cortex potentiated the subsequent rTMS to the M1 and produced MEP facilitation in PD patients but only when they were on medications (Suppa et al. 2010). The application of dorsal premotor cortical stimulation alone for PD patients has also been reported. Five Hz rTMS over premotor cortex facilitates MEP in healthy controls but not in PD patients off medications. After levodopa administration, the facilitatory effect of premotor cortical stimulation was restored (Mir et al. 2005). On the other hand, 1 Hz rTMS over dorsal premotor cortex decreased the SICI in healthy controls but increased SICI in PD off medications. Single dose of levodopa normalized the post-stimulation effect in PD patients (Buhmann et al. 2004). Although none of these studies reported significant improvement in motor symptoms by dorsal premotor cortical rTMS either in on or off medication states, these findings suggest that it is worthy of further investigations in the treatment of PD.

12.3 Dystonia

Most TMS studies in dystonia were carried out in focal dystonia. They have revealed pathophysiological abnormalities in the motor cortical areas in dystonia.

12.3.1 Motor Evoked Potential

12.3.1.1 MEP Latency and CMCT

MEP latency and CMCT are normal for focal dystonia both in hand (Schwenkreis et al. 1999) and cranial muscles (Hanajima et al. 1998). These results suggest that conduction in the motor pathways is not impaired in focal dystonia. On the other hand, shortened MEP latency has been found in the sternocleidomastoid muscles on both the affected and unaffected sides for cervical dystonia (Odergren et al. 1997).

12.3.1.2 MEP Threshold and Amplitude

Rest motor threshold (RMT) and active motor threshold (AMT) are normal in dystonia, and are unchanged after rTMS (Siebner et al. 1999a). MEP amplitude is normal at rest but during muscle contraction the slope of the recruitment curve may be steeper in dystonia patients than in controls (Ikoma et al. 1996).

12.3.2 Silent Period

Silent Period (SP) duration induced with high stimulus intensity is shorter in focal hand and arm dystonia patients than in healthy controls (Mavroudakis et al. 1995; Chen et al. 1997). In patients with writer's cramp, the shortened SP is more pronounced during dystonic contraction than that during voluntary contraction with comparable EMG activity (Filipovic et al. 1997). In addition, bilateral reduction of SP duration has been found in patients with unilateral symptoms (Rona et al. 1998). In patients with blepharospasm or oro-mandibular dystonia, the shortened SP duration has been recorded in the orbicularis oculi and perioral muscles. The SP is even shorter in patients with dystonia affecting both upper and lower facial muscles (Curra et al. 2000).

12.3.3 Intracortical Circuits

12.3.3.1 Short and Long Interval Intracortical Inhibitions

Bilateral reduction of SICI has been reported in patients with writer's cramp (Ridding et al. 1995b). Similar reduction in SICI was found in other types of dystonia affecting upper limb muscles and this reduction is normalized by botulinum toxin at 1 month after injection (Gilio et al. 2000). However, the effect of botulinum toxin on SICI was not confirmed in pure writer's cramp (Boroojerdi et al. 2003). In addition, TMS current in the reversed (anterior–posterior) direction may not detect reduced SICI in focal hand dystonia patients while SICI measured with both the regular (posterior–anterior) and the reversed current directions in cortical myoclonus is weaker than that in controls (Hanajima et al. 2008). These findings suggest that different sets of cortical interneurons may be impaired in focal dystonia and cortical myoclonus because TMS in different current directions activates separate subgroups of interneurons in the M1 (Di Lazzaro et al. 2004; Ni et al. 2011). Active LICI is impaired in writer's cramp (Chen et al. 1997). Interestingly, reduction in SICI and LICI was also found in patients with psychogenic dystonia (Espay et al. 2006).

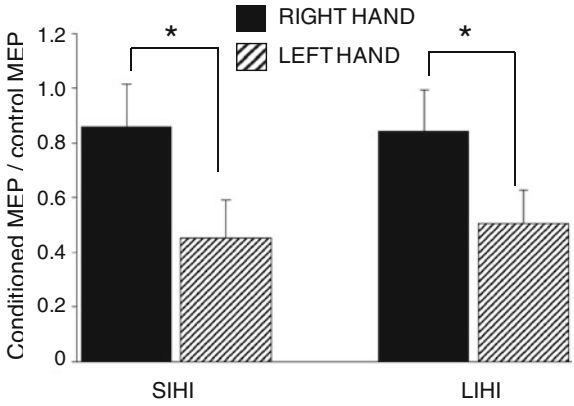


Fig. 12.4 Interhemispheric inhibition in writer's cramp. SIHI and LIHI were investigated with paired-pulse TMS at interstimulus intervals of 10 and 50 ms in seven writer's cramp patients with right hand symptoms. Conditioned MEP amplitude was expressed as a ratio to the MEP amplitude generated by test stimulus alone (control). The values are below 1, indicating inhibition. Both SIHI and LIHI in the affected hand (black columns) were reduced compared to unaffected hand (striped columns). *LIHI* long latency interhemispheric inhibition; *SIHI* short latency interhemispheric inhibition. $*P < 0.05$, comparing right hand to the left hand. Modified from Nelson et al. (2010)

12.3.3.2 Interhemispheric Interaction and Afferent Inhibition

Reduced SIHI and LIHI have been reported in writer's cramp. Figure 12.4 shows the results from a group of writer's cramp patients without mirror dystonia with the right hand affected. Resting SIHI and LIHI from unaffected side to the affected side were decreased compared to the same measurements from the affected to the unaffected side. During a pen holding task there was no difference in either SIHI or LIHI between patients and healthy controls (Nelson et al. 2010). In contrast, it was reported that SIHI was reduced in focal hand dystonia patients with mirror dystonia during premovement phase of a motor task (Beck et al. 2009). Modulation of cortical excitability by contralateral dorsal premotor cortex stimulation is also impaired in focal hand dystonia. A stimulus with intensity of 90–130 % RMT applied to the contralateral premotor cortex inhibits the M1 8 or 10 ms later in healthy controls. Such modulation was reduced in focal hand dystonia. However, the facilitation induced by a stimulus with 70–90 % AMT to the contralateral premotor cortex 6 or 8 ms prior to M1 stimulation did not change in dystonia (Koch et al. 2008). SAI is normal in both psychogenic and organic dystonia (Quartarone et al. 2009).

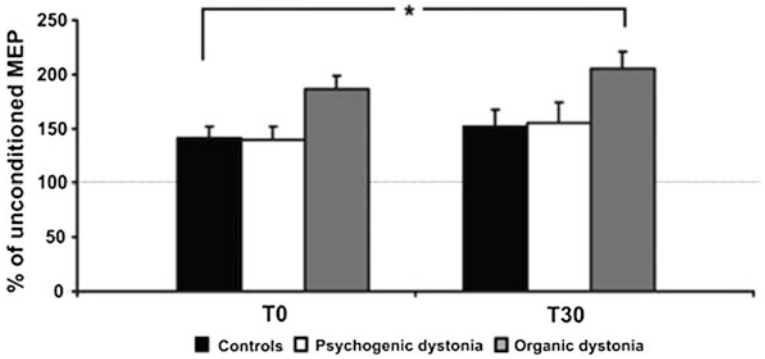


Fig. 12.5 Cortical plasticity in psychogenic and organic dystonia. The cortical plasticity generated by PAS was tested in 10 patients with organic dystonia (*gray column*), 10 patients with definite or probable psychogenic dystonia (*white column*), and 10 healthy controls (*black column*). The ordinate indicates the MEP amplitude after PAS expressed as a percentage of the MEP amplitude before PAS (baseline, shown in *dash line*). The effect of PAS on motor cortical excitability was measured immediately after PAS (T0) and 30 min after PAS (T30). The asterisk indicates a significant interaction between time and group with $P = 0.003$. *PAS* paired associative stimulation. Modified from Quartarone et al. (2009)

12.3.4 Cortical Plasticity in Dystonia

PAS induced plastic changes are exaggerated in organic dystonia. The increase in MEP amplitude induced by PAS was larger in organic dystonia than in healthy controls (Fig. 12.5). On the other hand, the increase in MEP amplitude with PAS was similar for psychogenic dystonia and healthy controls (Quartarone et al. 2009) (Fig. 12.5), suggesting that the pathophysiologic mechanisms for organic and psychogenic dystonia are different. The response to PAS may be able to distinguish between organic and psychogenic dystonia because measurements of intracortical circuits including SICI, LICI (reduced) and SAI (normal) are similar in organic and psychogenic dystonia, but this needs to be evaluated further. In this regard, it has been argued that the steeper MEP recruitment curve in organic dystonia may explain the difference between two patient groups (Rosenkranz 2010) since the slope of the recruitment curve may be steeper in dystonia patients than in controls during muscle contraction (Ikoma et al. 1996). The abnormal plasticity induced by PAS in organic dystonia may be normalized by internal globus pallidus DBS. It was reported that the effects of DBS occurred within 1 month of DBS before the achievement of full clinical benefit but there was considerable individual variation in the long-term effects of DBS on PAS (Ruge et al. 2011).

12.3.5 Repetitive Transcranial Magnetic Stimulation in Dystonia

One study showed that subthreshold 1 Hz rTMS transiently improved dystonic symptoms in writer's cramp with reduced writing pressure (Siebner et al. 1999b). This improvement is companied by normalization of SICI, SP duration, and MEP intensity recruitment curve. In contrast, superthreshold 1 Hz rTMS increases MEP size in writer's cramp while the same protocol decreases MEP size in healthy controls (Siebner et al. 1999a), indicating that the response to rTMS is abnormal in dystonia. The abnormal response to inhibitory rTMS in writer's cramp was also confirmed by continuous theta burst stimulation applied to dorsal premotor cortex. Continuous theta burst stimulation decreased MEP amplitudes in healthy subjects but not in patients with writer's cramp. Interestingly, such stimulation normalized the decreased SICI and improved the motor symptoms and writing speeds in patients (Huang et al. 2010).

12.4 Essential Tremor

The origin of essential tremor (ET) is unknown. One hypothesis is that abnormal oscillations originate in the inferior olive. The output of inferior olive is transmitted to the cerebellum via the climbing fibers. The abnormal oscillations may then be transferred to the cortex via the cerebellothalamocortical pathway (Deuschl et al. 2000; Pinto et al. 2003).

12.4.1 Single- and Paired-Pulse TMS Measurements

Patients with ET have normal CMCT, SP duration, SICI and LICI (Romeo et al. 1998). CBI is also normal in ET (Pinto et al. 2003), suggesting that the cerebellar output pathway is normal in ET but the findings are consistent with abnormal input to the cerebellum.

12.4.2 Tremor Reset

ET is reset by mechanical perturbations (Lee and Stein 1981). PD postural tremor is not reset by this type of stimulation and this may be useful for distinguishing these two types of tremor. TMS applied to M1 resets both PD postural tremor and ET. However, the time to reoccurrence of rhythmic EMG activity varied with the duration of tremor burst in PD postural tremor but not with that of ET. TMS shortened the duration of tremor burst in PD postural tremor but had no influence

on the duration in ET (Britton et al. 1993). In addition, TMS over the cerebellum did not reset ET (Pinto et al. 2003).

12.4.3 Repetitive Transcranial Magnetic Stimulation in ET

Low-frequency superthreshold rTMS of the cerebellum has been reported to induce short lasting (less than 1 h) improvement in ET with both clinical and accelerometric measures (Gironell et al. 2002). However, it has been argued that some of the effects may be mediated by activation of peripheral nerves and muscles (Gerschlager et al. 2002).

12.5 Tourette's Syndrome

Tourette's syndrome is a neuropsychiatric disorder in which cortical disinhibition has been proposed as a pathophysiologic mechanism involved in the generation of tics. Tics are typically reduced during task performance and concentration.

The motor threshold is normal in Tourette's syndrome, suggesting that motor cortical membrane excitability is unchanged. The slope of MEP recruitment curve is shallower in untreated patients than in the healthy controls at rest. During voluntary muscle contraction, the slope becomes normal in patients (Orth et al. 2008). SIHI from the left to right M1 (CS on left M1, TS on right M1) is weaker in this group of patients compared to control but SIHI measured in the opposite direction is normal. In addition, the significant correlation between SIHI and fractional anisotropy from left to right M1 seen in healthy controls was not observed in untreated patients with Tourette's syndrome (Baumer et al. 2010). SP is shortened and SICI is reduced in Tourette's syndrome, suggesting that synaptic connectivity may be impaired. These abnormalities were found in untreated patients in whom the tics involved the target muscle used for TMS (Ziemann et al. 1997). The normal motor threshold and reduced resting SICI in Tourette's syndrome have been confirmed by a recent study with a well-designed protocol (Heise et al. 2010). These measurements were also tested in a functional context when subjects performed a simple reaction time task. During the pre-movement period MEP amplitude was lower in the patient than that in the control group (Fig. 12.6a). More importantly, reduced SICI at rest in patients increased quickly and achieved the normal range at about 50 % of reaction time (Fig. 12.6b). These results are consistent with the findings in Tourette's syndrome that tics are pronounced at rest and are reduced during task performance because the increased SICI during the task performance restores normal cortical inhibition. The reduced MEP amplitude during task performance may be explained by the very quick increase in SICI that inhibits the corticospinal output.

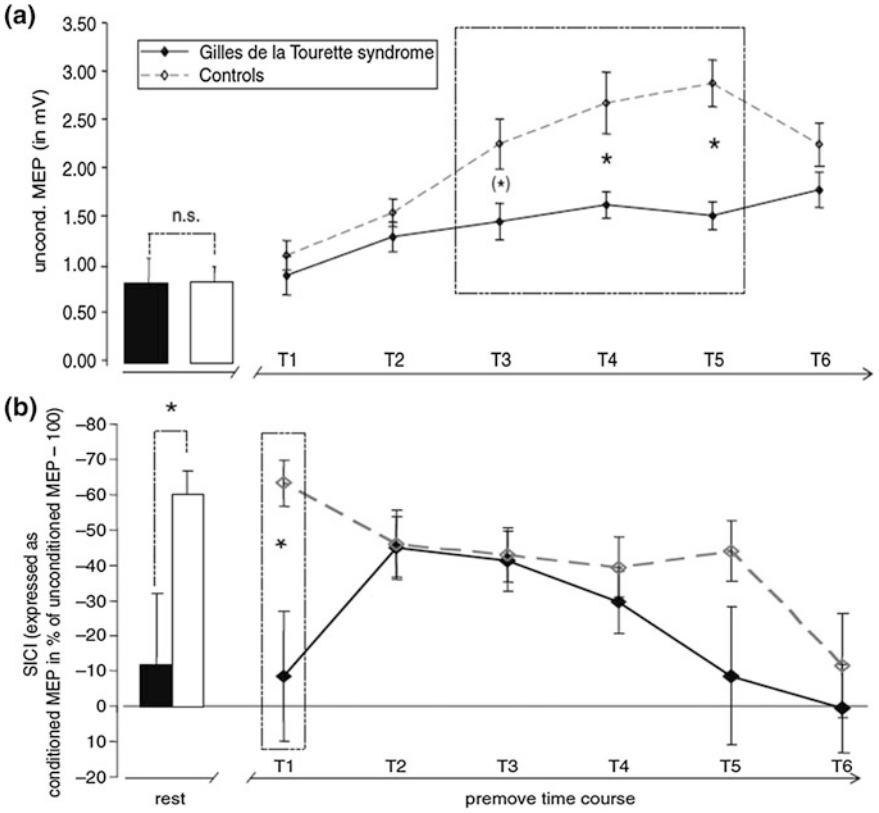


Fig. 12.6 Motor cortical excitability and short interval intracortical inhibition in Tourette's syndrome. The abscissa indicates the time points during the premovement period when the subjects performed a simple reaction time task. The data from 11 patients with Tourette's syndrome (filled points with *solid line* and *black columns*) were compared to 11 healthy controls (open points with *dash line* and *white columns*). Time points T1–T6 refers to 40, 50, 60, 70, 80, 100 % of reaction time. The measurements at these time points were compared to measurements at rest (columns on the left side). Reaction time was measured without applying TMS. **a** MEP amplitude elicited with single-pulse TMS. There was no difference between patients and controls at rest. However, MEP amplitudes were lower in patient group than that in the control group at time points T3–T5 during the premovement period. **b** SICI elicited by paired-pulse TMS. It is expressed as the difference between conditioned MEP amplitude and test MEP amplitude and this difference was normalized as a percentage of the test MEP amplitude. Negative values indicate inhibition. There was significantly less SICI in patients than in healthy controls at rest and at the early phase (T1) during reaction time. SICI at the late phases during reaction time in the patients was normal. $*P < 0.05$, comparison between patients and healthy controls. The significant differences are emphasized in the panels. *SICI* short interval intracortical inhibition. Modified from Heise et al. (2010)

12.6 Future Directions

In this chapter, we reviewed the changes in motor cortical functions demonstrated with TMS which helped to elucidate the pathophysiology of movement disorders. Several important points should be taken into account in the interpretation of the results. First, studies with single-, paired-, and triple-pulse TMS usually compared MEP amplitudes between patients and healthy controls. Findings in patients that are different from controls are considered abnormal. However, if the MEPs are mediated by different neural elements in patients and controls, single pulse TMS studies may not distinguish the abnormality in patients. Second, most paired- or triple-pulse TMS studies assumed that the same cortical circuits are used to activate corticospinal neurons and produce MEP in patients and controls. However, if TMS activates different cortical circuits in patients and controls (e.g. circuits responsible for I1 vs. I3 waves) that have different susceptibility to cortical inhibition, this may result in apparent abnormalities in cortical inhibition without any "real" change in cortical inhibition caused by the disease. In addition, many TMS studies investigated intracortical circuits only at a single ISI and stimulus intensity which may miss potential changes. Therefore, future studies using a range of stimulus intensities, ISIs, and current directions, and different recording methods such as epidural or single motor unit recordings that can test different direct and indirect waves will address some of these issues and further improve our understanding of pathophysiology of the underlying diseases.

While rTMS within established guidelines is safe for the patients with movement disorders, the benefit is generally short-lived with single sessions of rTMS. Multiple sessions of rTMS may extend the clinical benefit but whether this can achieve the magnitude of benefit seen with pharmacologic treatments remains to be established. rTMS will most likely be used as an adjunctive therapy for movement disorders but is not likely to alter the underlying pathologic processes. Future studies will need to develop rTMS into a practical treatment with large, sham-controlled studies, introduce new stimulus parameters and examine whether rTMS can be combined with other treatments to generate long-term therapeutic benefits for movement disorders.

References

Abbruzzese G, Marchese R, Trompetto C (1997) Sensory and motor evoked potentials in multiple system atrophy: a comparative study with Parkinson's disease. Mov Disord 12:315–321

Ashby P, Paradiso G, Saint-Cyr J, Chen R, Lang A, Lozano A (2001) Potentials evoked at the scalp by stimulation near the human subthalamic nucleus. Clin Neurophysiol 112:431–437

Barker AT, Jalinous R, Freeston IL (1985) Non-invasive stimulation of the human motor cortex. Lancet II:1106–1107

Baumer T, Thomalla G, Kroeger J et al (2010) Interhemispheric motor networks are abnormal in patients with Gilles de la Tourette syndrome. Mov Disord 25:2828–2837

Beck S, Shamim EA, Richardson SP, Schubert M, Hallett M (2009) Inter-hemispheric inhibition is impaired in mirror dystonia. Eur J Neurosci 29:1634–1640

Benninger DH, Berman BD, Houdayer E et al (2011) Intermittent theta-burst transcranial magnetic stimulation for treatment of Parkinson disease. Neurology 76:601–609

Berardelli A, Rona S, Inghilleri M, Manfredi M (1996) Cortical inhibition in Parkinson's disease. A study with paired magnetic stimulation. Brain 119:71–77

Boroojerdi B, Cohen LG, Hallett M (2003) Effects of botulinum toxin on motor system excitability in patients with writer's cramp. Neurology 61:1546–1550

Britton TC, Thompson PD, Day BL, Rothwell JC, Findley LJ, Marsden CD (1993) Modulation of postural wrist tremors by magnetic stimulation of the motor cortex in patients with Parkinson's disease or essential tremor and in normal subjects mimicking tremor. Ann Neurol 33:473–479

Buhmann C, Gorsler A, Baumer T et al (2004) Abnormal excitability of premotor-motor connections in de novo Parkinson's disease. Brain 127:2732–2746

Cantello R, Gianelli M, Bettucci D, Civardi C, DeAngelis MS, Mutani R (1991) Parkinson's disease rigidity: magnetic motor evoked potentials in a small hand muscle. Neurology 91:1449–1456

Cantello R, Tarletti R, Civardi C (2002) Transcranial magnetic stimulation and Parkinson's disease. Brain Res Brain Res Rev 38:309–327

Chen R, Wassermann EM, Caños M, Hallett M (1997) Impaired inhibition in writer's cramp during voluntary muscle activation. Neurology 49:1054–1059

Chen R, Tam A, Bütefisch C et al (1998) Intracortical inhibition and facilitation in different representations of the human motor cortex. J Neurophysiol 80:2870–2881

Chen R, Corwell B, Hallett M (1999) Modulation of motor cortex excitability by median nerve and digit stimulation. Exp Brain Res 129:77–86

Chen R, Garg RR, Lozano AM, Lang AE (2001) Effects of internal globus pallidus stimulation on motor cortex excitability. Neurology 56:716–723

Chen R, Cros D, Curra A et al (2008) The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 119:504–532

Chu J, Wagle-Shukla A, Gunraj C, Lang AE, Chen R (2009) Impaired presynaptic inhibition in the motor cortex in Parkinson disease. Neurology 72:842–849

Cunic D, Roshan L, Khan FI, Lozano AM, Lang AE, Chen R (2002) Effects of subthalamic nucleus stimulation on motor cortex excitability in Parkinson's disease. Neurology 58:1665–1672

Curra A, Romaniello A, Berardelli A, Cruccu G, Manfredi M (2000) Shortened cortical silent period in facial muscles of patients with cranial dystonia. Neurology 54:130–135

Dauper J, Peschel T, Schrader C et al (2002) Effects of subthalamic nucleus (STN) stimulation on motor cortex excitability. Neurology 59:700–706

Deuschl G, Wenzelburger R, Loffler K, Raethjen J, Stolze H (2000) Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. Brain 123(Pt 8): 1568–1580

Di Lazzaro V, Oliviero A, Profice P et al (2000) Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex. Exp Brain Res 135:455–461

Di Lazzaro V, Oliviero A, Pilato F et al (2004) The physiological basis of transcranial motor cortex stimulation in conscious humans. Clin Neurophysiol 115:255–266

Di Lazzaro V, Pilato F, Dileone M, Tonali PA, Ziemann U (2005) Dissociated effects of diazepam and lorazepam on short-latency afferent inhibition. J Physiol 569:315–323

Edwards MJ, Talelli P, Rothwell JC (2008) Clinical applications of transcranial magnetic stimulation in patients with movement disorders. Lancet Neurol 7:827–840

Elahi B, Elahi B, Chen R (2009) Effect of transcranial magnetic stimulation on Parkinson motor function–systematic review of controlled clinical trials. Mov Disord 24:357–363

Ellaway PH, Davey NJ, Maskill DW, Dick JP (1995) The relation between bradykinesia and excitability of the motor cortex assessed using transcranial magnetic stimulation in normal and parkinsonian subjects. Electroencephalogr Clin Neurophysiol 97:169–178
Espay AJ, Morgante F, Purzner J, Gunraj CA, Lang AE, Chen R (2006) Cortical and spinal abnormalities in psychogenic dystonia. Ann Neurol 59:825–834
Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. J Physiol (Lond) 453:525–546
Filipovic SR, Ljubisavljevic M, Svetel M, Milanovic S, Kacar A, Kostic VS (1997) Impairment of cortical inhibition in writer's cramp as revealed by changes in electromyographic silent period after transcranial magnetic stimulation. Neurosci Lett 222:167–170
Filipovic SR, Rothwell JC, van de Warrenburg BP, Bhatia K (2009) Repetitive transcranial magnetic stimulation for levodopa-induced dyskinesias in Parkinson's disease. Mov Disord 24:246–253
Gerschlager W, Christensen LO, Bestmann S, Rothwell JC (2002) rTMS over the cerebellum can increase corticospinal excitability through a spinal mechanism involving activation of peripheral nerve fibres. Clin Neurophysiol 113:1435–1440
Gilio F, Curra A, Lorenzano C, Modugno N, Manfredi M, Berardelli A (2000) Effects of botulinum toxin type A on intracortical inhibition in patients with dystonia. Ann Neurol 48:20–26
Gironell A, Kulisevsky J, Lorenzo J, Barbanoj M, Pascual-Sedano B, Otermin P (2002) Transcranial magnetic stimulation of the cerebellum in essential tremor: a controlled study. Arch Neurol 59:413–417
Hallett M (2007) Transcranial magnetic stimulation: a primer. Neuron 55:187–199
Hallett M, Deuschl G (2010) Are we making progress in the understanding of tremor in Parkinson's disease? Ann Neurol 68:780–781
Hamada M, Ugawa Y, Tsuji S (2008) High-frequency rTMS over the supplementary motor area for treatment of Parkinson's disease. Mov Disord 11:1524–1531
Hanajima R, Ugawa Y, Terao Y et al (1998) Cortico-cortical inhibition of the motor cortical area projecting to sternocleidomastoid muscle in normals and patients with spasmodic torticollis or essential tremor. Electroencephalogr Clin Neurophysiol 109:391–396
Hanajima R, Okabe S, Terao Y et al (2008) Difference in intracortical inhibition of the motor cortex between cortical myoclonus and focal hand dystonia. Clin Neurophysiol 119:1400–1407
Heise KF, Steven B, Liuzzi G et al (2010) Altered modulation of intracortical excitability during movement preparation in Gilles de la Tourette syndrome. Brain 133:580–590
Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005) Theta burst stimulation of the human motor cortex. Neuron 45:201–206
Huang YZ, Rothwell JC, Lu CS, Wang J, Chen RS (2010) Restoration of motor inhibition through an abnormal premotor-motor connection in dystonia. Mov Disord 25:696–703
Huang YZ, Rothwell JC, Lu CS, Chudakov B, Chen RS (2011) Abnormal bidirectional plasticity-like effects in Parkinson's disease. Brain 134:2312–2320
Ikoma K, Samii A, Mercuri B, Wassermann EM, Hallett M (1996) Abnormal cortical motor excitability in dystonia. Neurology 46:1371–1376
Jankovic J, Schwartz KS, Ondo W (1999) Re-emergent tremor of Parkinson's disease. J Neurol Neurosurg Psychiatry 67:646–650
Koch G, Schneider S, Baumer T et al (2008) Altered dorsal premotor-motor interhemispheric pathway activity in focal arm dystonia. Mov Disord 23:660–668
Koch G, Brusa L, Carrillo F et al (2009) Cerebellar magnetic stimulation decreases levodopa-induced dyskinesias in Parkinson disease. Neurology 73:113–119
Kujirai T, Caramia MD, Rothwell JC et al (1993) Corticocortical inhibition in human motor cortex. J Physiol (Lond) 471:501–519
Kuriakose R, Saha U, Castillo G et al (2010) The nature and time course of cortical activation following subthalamic stimulation in Parkinson's disease. Cereb Cortex 20:1926–1936

Lang AE, Lozano AM (1998) Parkinson's disease. First of two parts. N Engl J Med 339:1044–1053

Lee RG, Stein RB (1981) Resetting of tremor by mechanical perturbations: a comparison of essential tremor and parkinsonian tremor. Ann Neurol 10:523–531

Li JY, Espay AJ, Gunraj CA et al (2007) Interhemispheric and ipsilateral connections in Parkinson's disease: relation to mirror movements. Mov Disord 22:813–821

MacKinnon CD, Gilley EA, Weis-McNulty A, Simuni T (2005) Pathways mediating abnormal intracortical inhibition in Parkinson's disease. Ann Neurol 58:516–524

Mavroudakis N, Caroyer JM, Brunko E, Zegers de Beyl D (1995) Abnormal motor evoked responses to transcranial magnetic stimulation in focal dystonia. Neurology 45:1671–1677

Mir P, Matsunaga K, Gilio F, Quinn NP, Siebner HR, Rothwell JC (2005) Dopaminergic drugs restore facilitatory premotor-motor interactions in Parkinson disease. Neurology 64:1906–1912

Morgante F, Espay AJ, Gunraj C, Lang AE, Chen R (2006) Motor cortex plasticity in Parkinson's disease and levodopa-induced dyskinesias. Brain 129:1059–1069

Nelson AJ, Hoque T, Gunraj C, Ni Z, Chen R (2010) Impaired interhemispheric inhibition in writer's cramp. Neurology 75:441–447

Ni Z, Gunraj C, Nelson AJ et al (2009) Two phases of interhemispheric inhibition between motor related cortical areas and the primary motor cortex in human. Cereb Cortex 19:1654–1665

Ni Z, Pinto AD, Lang AE, Chen R (2010) Involvement of the cerebellothalamocortical pathway in Parkinson disease. Ann Neurol 68:816–824

Ni Z, Charab S, Gunraj C et al (2011) Transcranial magnetic stimulation in different current directions activates separate cortical circuits. J Neurophysiol 105:749–756

Odergren T, Rimpilainen I, Borg J (1997) Sternocleidomastoid muscle responses to transcranial magnetic stimulation in patients with cervical dystonia. Electroencephalogr Clin Neurophysiol 105:44–52

Okabe S, Ugawa Y, Kanazawa I (2003) 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's disease. Mov Disord 18:382–388

Orth M, Munchau A, Rothwell JC (2008) Corticospinal system excitability at rest is associated with tic severity in Tourette syndrome. Biol Psychiatry 64:248–251

Pascual-Leone A, Valls-Sole J, Toro C, Wassermann EM, Hallett M (1994) Resetting of essential tremor and postural tremor in Parkinson's disease with transcranial magnetic stimulation. Muscle Nerve 17:800–807

Peurala SH, Muller-Dahlhaus JF, Arai N, Ziemann U (2008) Interference of short-interval intracortical inhibition (SICI) and short-interval intracortical facilitation (SICF). Clin Neurophysiol 119:2291–2297

Pinto AD, Chen R (2001) Suppression of the motor cortex by magnetic stimulation of the cerebellum. Exp Brain Res 140:505–510

Pinto AD, Lang AE, Chen R (2003) The cerebellothalamocortical pathway in essential tremor. Neurology 60:1985–1987

Priori A, Berardelli A, Inghilleri M, Accornero N, Manfredi M (1994) Motor cortical inhibition and the dopaminergic system. Pharmacological changes in the silent period after transcranial magnetic brain stimulation in normal subjects, patients with Parkinson's disease and drug-induced parkinsonism. Brain 117:317–323

Quartarone A, Rizzo V, Terranova C et al (2009) Abnormal sensorimotor plasticity in organic but not in psychogenic dystonia. Brain 132:2871–2877

Ridding MC, Inzelberg R, Rothwell JC (1995a) Changes in excitability of motor cortical circuitry in patients with Parkinson's disease. Ann Neurol 37:181–188

Ridding MC, Sheean G, Rothwell JC, Inzelberg R, Kujirai T (1995b) Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. J Neurol Neurosurg Psychiatry 39:493–498

Romeo S, Berardelli A, Pedace F, Inghilleri M, Giovannelli M, Manfredi M (1998) Cortical excitability in patients with essential tremor. Muscle Nerve 21:1304–1308

Rona S, Berardelli A, Vacca L, Inghilleri M, Manfredi M (1998) Alterations of motor cortical inhibition in patients with dystonia. Mov Disord 13:118–124

Rosenkranz K (2010) Plasticity and intracortical inhibition in dystonia–methodological reconsiderations. Brain 133:e146

Rossini PM, Barker AT, Berardelli A et al (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 91:79–92

Rothwell JC (1997) Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. J Neurosci Methods 74:113–122

Ruge D, Tisch S, Hariz MI et al (2011) Deep brain stimulation effects in dystonia: time course of electrophysiological changes in early treatment. Mov Disord 26:1913–1921

Sailer A, Molnar GF, Paradiso G, Gunraj CA, Lang AE, Chen R (2003) Short and long latency afferent inhibition in Parkinson's disease. Brain 126:1883–1894

Sailer A, Cunic DI, Paradiso GO et al (2007) Subthalamic nucleus stimulation modulates afferent inhibition in Parkinson disease. Neurology 68:356–363

Sanger TD, Garg RR, Chen R (2001) Interactions between two different inhibitory systems in the human motor cortex. J Physiol (Lond) 530:307–317

Sax DS, Jonhson TL, Feldman RG (1977) L-Dopa effects on H-reflex recovery in Parkinson's disease. Ann Neurol 2:120–124

Schneider SA, Talelli P, Cheeran B et al (2008) Motor cortical physiology in patients and asymptomatic carriers of parkin gene mutations. Mov Disord 13:1812–1819

Schwenkreis P, Vorgerd M, Malin JP, Tegenthoff M (1999) Assessment of postexcitatory inhibition in patients with focal dystonia. Acta Neurol Scand 100:260–264

Shirota Y, Hamada M, Hanajima R et al (2010) Cerebellar dysfunction in progressive supranuclear palsy: a transcranial magnetic stimulation study. Mov Disord 25:2413–2419

Siebner HR, Dressnandt J, Auer C, Conrad B (1998) Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. Muscle Nerve 21:1209–1212

Siebner HR, Auer C, Conrad B (1999a) Abnormal increase in the corticomotor output to the affected hand during repetitive transcranial magnetic stimulation of the primary motor cortex in patients with writer's cramp. Neurosci Lett 262:133–136

Siebner HR, Tormos JM, Ceballos-Baumann AO et al (1999b) Low frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. Neurology 52:529–537

Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J (2000) Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 123:572–584

Strafella AP, Paus T, Fraraccio M, Dagher A (2003) Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain 126:2609–2615

Strafella AP, Ko JH, Monchi O (2006) Therapeutic application of transcranial magnetic stimulation in Parkinson's disease: the contribution of expectation. Neuroimage 31:1666–1672

Suppa A, Iezzi E, Conte A et al (2010) Dopamine influences primary motor cortex plasticity and dorsal premotor-to-motor connectivity in Parkinson's disease. Cereb Cortex 20:2224–2233

Suppa A, Marsili L, Belvisi D et al (2011) Lack of LTP-like plasticity in primary motor cortex in Parkinson's disease. Exp Neurol 227:296–301

Tokimura H, Di Lazzaro V, Tokimura Y et al (2000) Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol (Lond) 523:503–513

Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I (1995) Magnetic stimulation over the cerebellum in humans. Ann Neurol 37:703–713

Valls-Sole J, Pascual-Leone A, Brasil-Neto JP, Cammarota A, McShane L, Hallett M (1994) Abnormal facilitation of the response to transcranial magnetic stimulation in patients with Parkinson's disease. Neurology 44:735–741

Valls-Solé J, Pascual-Leone A, Wassermann EM, Hallett M (1992) Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr Clin Neurophysiol 85:355–364

Valzania F, Strafella AP, Quatrale R et al (1997) Motor evoked responses to paired cortical magnetic stimulation in Parkinson's disease. Electroencephalogr Clin Neurophysiol 105:37–43

Wagle-Shukla A, Angel MJ, Zadikoff C et al (2007) Low-frequency repetitive transcranial magnetic stimulation for treatment of levodopa-induced dyskinesias. Neurology 68:704–705

Wassermann EM (1998) Risk and safety in repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 108:1–16

Wassermann EM, Samii A, Mercuri B et al (1996) Responses to paired transcranial magnetic stimuli in resting, active, and recently activated muscle. Exp Brain Res 109:158–163

Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J (1999) Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J Physiol (Lond) 517:591–597

Zamir O, Gunraj C, Ni Z, Mazzella F, Chen R (2012) Effects of theta burst stimulation on motor cortex excitability in Parkinson's disease. Clin Neurophysiol 123:815–823

Ziemann U, Paulus W, Rothenberger A (1997) Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. Am J Psychiatry 154:1277–1284

Chapter 13
Stroke

Cathy M. Stinear and Winston D. Byblow

Abstract Stroke causes lesions that affect both grey and white matter in the brain, typically in one hemisphere. The resulting impairments are due to loss of function at the site of the lesion, as well as loss of functional connectivity between the lesion site and other parts of the central nervous system. Stroke, therefore, perturbs networks responsible for a range of functions, in both the ipsilesional and contralesional hemispheres. This chapter reviews the effects of stroke on networks responsible for voluntary motor activity, language and spatial attention. Asymmetric interhemispheric inhibition between homologous cortical network nodes is a common theme across these functional domains. Recovery after stroke requires reorganisation within the affected networks, and is limited by the extent of damage to connections between essential network nodes. Recruitment of existing or new nodes in the network, in either hemisphere, influences recovery of function, particularly at the sub-acute stage. However, the best recovery of function occurs with normalisation of network activity. After stroke, non-invasive brain stimulation can be used to either enhance or suppress activity of specific cortical nodes, and the functional connectivity between target and remote areas. The effective use of stimulation techniques with individual patients can be guided by measures of the activity and connectivity in the network of interest.

13.1 Introduction

Stroke is a leading cause of adult disability and mortality (Mackay et al. 2004), affecting one in six people at some point in their lives (Seshadri et al. 2006). Most strokes are ischaemic, causing infarction of grey and white matter in the territory

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supplied by the blocked artery. Each episode of stroke typically produces a lesion that is lateralised to one hemisphere or the other. This disrupts the functional connectivity of networks within both the ipsilesional and contralesional hemispheres, and between the two hemispheres. Stroke can affect networks responsible for various functions, and the resulting impairments can reveal much about relationships between the nodes of these networks. This chapter reviews how stroke affects the function of motor, language and attention networks and the potential application of non-invasive brain stimulation techniques to modify the connectivity in these networks for therapeutic benefit.

13.2 Motor System

13.2.1 Ipsilesional Connectivity

In humans, the predominant descending motor pathway is the lateral corticospinal tract (CST), connecting primary motor cortex (M1) with alpha motoneurons in the spinal cord, two vital nodes of the central nervous system network for voluntary movement. The importance of the lateral CST is most clearly understood in terms of upper limb impairment and recovery after stroke. The lateral CST is considered to be a crossed pathway, in keeping with the clinical findings that unilateral damage leads to a contralateral paresis and, in some cases, paralysis. Most patients are unable to carry out fine motor activities with the affected hand after complete injury of the lateral CST (Davidoff 1990).

The functional integrity of the CST can be assessed by using transcranial magnetic stimulation (TMS) to elicit motor evoked potentials (MEPs) in paretic limb muscles, and this might provide useful prognostic information early after stroke, but the optimal timing of assessment is unclear (Catano et al. 1996; Heald et al. 1993; Trompetto et al. 2000). The structural integrity of the CST can be assessed with diffusion-weighted MRI (DW-MRI) measures such as fractional anisotropy, which is sensitive to white matter disruption. These techniques are complementary in that measures from both relate to upper limb impairment (Jang 2009; Schaechter et al. 2009; Stinear et al. 2007; Ward et al. 2007). These neurophysiological and neuroimaging measures of the CST can be added to clinical assessments of motor function in a step-wise manner to improve prediction of individual patients' recovery (Stinear 2010, Stinear et al. 2012).

A recent study used DW-MRI and tractography to identify a distinct descending pathway intermingled with the lateral CST at the level of the internal capsule, which then deviates toward the posterior pons (Lindenberg et al. 2009). This pathway may represent the cortico-reticulo-spinal or cortico-rubro-spinal tracts known to exist in mammals. Greater disruption of this pathway by stroke is associated with greater upper limb impairment, highlighting the potential importance of this "alternate" motor pathway. This finding indicates that brainstem

nuclei may be critical nodes in the voluntary motor network, with a putative role in motor recovery after damage to the lateral CST (Jankowska and Edgley 2006).

There is currently no strong consensus regarding the importance of the lateral CST in recovery of walking after stroke. One study has used DW-MRI to show that some patients with complete lesions to the lateral CST regain walking ability within 6 months of stroke (Ahn et al. 2006). However, this study did not examine functional integrity of the CST with TMS of leg motor cortex, so the extent to which the CST or alternate pathways between cortical and spinal nodes contributed to recovery of gait was not determined. In contrast, Pirion and colleagues found that TMS-evoked MEPs in tibialis anterior could predict walking outcomes for patients with complete lower limb palsy immediately after stroke. Patients with no recordable MEPs 1 month post-stroke never regained walking ability, whereas patients with MEPs regained independent gait at discharge (Piron et al. 2005). These findings indicate the importance of functional integrity of the CST for recovery of lower limb function.

While these examples are by no means exhaustive, they clearly show that the functional integrity of the CST is a primary determinant in outcomes related to motor recovery after stroke. Cortical reorganisation also plays an important role in recovery of both upper and lower limb function. The extent to which cortical reorganisation is lateralised to the ipsilesional hemisphere, occurs bilaterally, or is restricted to the contralesional hemisphere, probably depends in part on the degree of damage to the ipsilesional CST, as described below.

In addition to M1, the dorsal and ventral premotor cortex (PMd, PMv), supplementary motor areas (SMA) and cingulate cortex are motor network nodes with direct connections to upper limb alpha motoneurons via the anterior CST. Although the distribution of direct projections from secondary motor cortical regions is greater for proximal than distal muscle representations (Turton et al. 1996), there is evidence that cortical reorganisation in premotor and supplementary motor areas can contribute to recovery of hand function, perhaps via disinhibition-mediated plasticity (Clarkson et al. 2010; Sanes and Donoghue 2000). TMS mapping studies have shown that hand muscle representations in M1 are displaced posteriorly in patients with near-complete recovery of hand function at the chronic stage after subcortical stroke (Byrnes et al. 2001; Rossini et al. 1998). There was a strong positive correlation between the magnitude of the map shift and grip strength in the patients' affected hands, indicating that cortical reorganisation after subcortical stroke is functionally significant (Byrnes et al. 2001). These shifts in cortical representations, which have also been observed using fMRI (Pineiro et al. 2001), indicate that cortical areas adjacent to M1 can contribute to the recovery of hand function, presumably through a long-term process involving unmasking of latent connections (Nudo 2003).

However, expansion of cortical representations through disinhibition processes may not always be desirable, and can also lead to poor outcomes. For example, Yao and colleagues examined brain connectivity with EEG, and upper limb kinematic and torque profiles, in patients at the chronic stage. They found that the degree of overlap between elbow and shoulder cortical representations correlated

with a loss of independent joint control (Yao et al. 2009). The extent to which disinhibition-mediated functional reorganisation may be adaptive or maladaptive is not completely understood, and may depend on the time frame of intracortical changes within the first few months after stroke (Swayne et al. 2008).

Another intriguing hypothesis is that upper limb recovery after stroke may be facilitated by an up-regulation of drive from corticospinal neurons in the ipsilesional premotor cortex to propriospinal neurons at the 3rd and 4th segments of the cervical spinal cord (C3/4). A relatively greater component of the descending command to paretic upper limb muscles is transmitted via presumed C3/4 propriospinal neurons in recovering stroke patients, compared to the unaffected limb (Mazevet et al. 2003; Stinear and Byblow 2004). Descending pathways to C3/4 neurons may originate in PMd, and this may explain why shifts in activation toward ipsilesional PMd might occur with affected hand task performance in fMRI studies (Calautti et al. 2010; Grefkes et al. 2010; James et al. 2009; O'Shea et al. 2007; Rehme et al. 2011a). In a recent study, activation strength within the ipsilesional PMd node scaled negatively with the functional integrity of the M1 CST assessed using TMS-derived MEPs in affected hand muscles, and residual grip strength (Ward et al. 2007). Based on the notion that ipsilesional PMd has a relatively large proportion of corticospinal neurons which exert control over alpha motoneurons innervating the proximal upper limb, the authors contended that the ipsilesional PMd activation might reflect activity in a new node contributing to upper limb recovery via the C3/4 propriospinal pathway.

13.2.2 Contralesional and Interhemispheric Connectivity

The primary motor cortex has sparse direct uncrossed connections to alpha motoneurons innervating ipsilateral distal hand muscles. Their functional importance is not well understood in adults, but their terminal branches are a readily available source from which sprouting could enhance actions of these neurons after injury to the crossed CST (Dum and Strick 1996; Jankowska and Edgley 2006). After stroke, the interplay between ipsilesional and contralesional M1 has been most extensively examined in the context of interhemispheric competition, or interhemispheric imbalance in M1 excitability. An increase in excitability of the contralesional M1, and reduced excitability of the ipsilesional M1, is common after stroke and most readily measured using TMS (Duque et al. 2005; Murase et al. 2004; Nowak et al. 2009; Traversa et al. 1998). There is also evidence from fMRI that increased contralesional hemisphere activity can occur during paretic upper limb movement, particularly in patients with greater damage to the ipsilesional CST and more severe upper limb impairment (Cramer et al. 1997; Lotze et al. 2006; Stinear et al. 2008; Ward et al. 2003, 2006, 2007). In patients with a severely impaired upper limb, excitability of contralesional M1 gradually increases with motor recovery, indicating that reorganisation towards the contralesional hemisphere may be an adaptive response in severely affected patients (Gerloff et al. 2006; see Fig. 13.1).

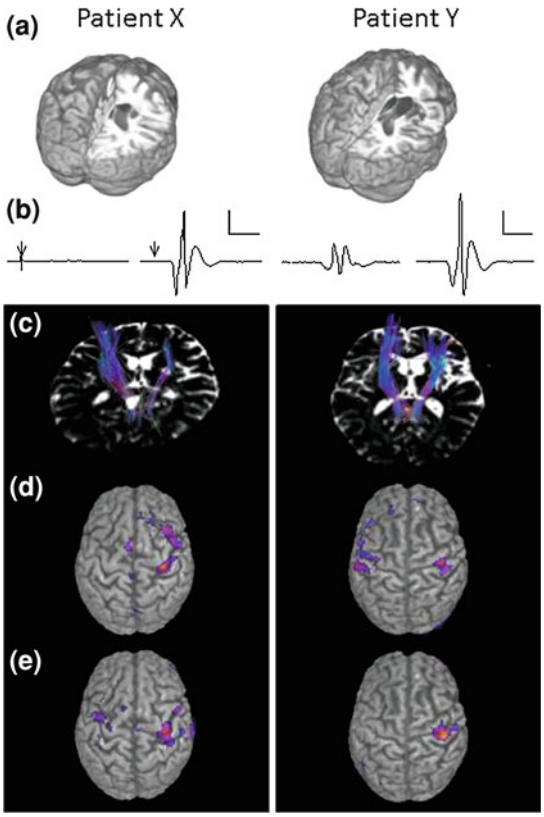

Fig. 13.1 After stroke, patterns of reorganisation within the motor network are constrained by the remaining functional connectivity between essential nodes, such as M1 and the spinal cord. **a** This is illustrated by data from two right hemisphere stroke patients who were scanned at 15 and 24 months, respectively, after subcortical infarction (Stinear et al. 2007). **b** Functional connectivity between M1 and the alpha motoneuron pool was assessed with single-pulse TMS. Patient X had no MEPs in the paretic forearm muscles, while Patient Y had MEPs that were smaller in amplitude compared to the non-paretic forearm. Calibration bars: 0.2 mV and 25 ms. **c** Diffusion weighted MRI data were used to reconstruct tracts seeded in the hand area of M1 and passing through the posterior limb of the internal capsule, indicating greater tract damage for Patient X than Patient Y, but with remaining connectivity for both. **d** BOLD signal during paretic hand opening/closing before 1 month of daily motor practice with the paretic upper limb. **e** After intervention, upper limb impairment decreased in both patients by the same amount (+4 points on the Fugl-Meyer scale). In Patient X, this improvement was accompanied by greater recruitment of contralesional motor network activity during paretic hand movement. In Patient Y, this improvement was accompanied by a shift towards more focal activity in the ipsilesional M1 node. Patient Y achieved a higher score at the study endpoint. Normalisation of motor network activity is more likely when functional connectivity between M1 and the spinal cord is largely preserved; however, widespread reorganisation of network activity can also result in beneficial compensation

The contralesional PMd has been implicated in assuming partial control over affected hand function in well-recovered stroke patients (Lotze et al. 2006), as well as in patients with greater impairment (Johansen-Berg et al. 2002). Both studies used a virtual lesion model, observing behavioural deficits arising as a result of single-pulse TMS of contralesional PMd. The extent to which upregulation of contralesional PMd is adaptive is not completely understood. The formation of new, or unmasking of latent, functional connections between the contralesional uncrossed anterior CST and the spinal cord may be maladaptive. For example, the descending commands through these weaker pathways may interfere at the level of the spinal cord with descending commands from the crossed lateral CST, particularly for proximal upper limb musculature. There is indirect evidence of this from Schwerin and colleagues, who demonstrated a positive correlation between the prevalence of ipsilateral MEPs from contralesional hemisphere TMS in the affected pectoralis major and upper limb impairment for patients at the chronic stage (Schwerin et al. 2008). For well-recovered patients, it seems unlikely that contralesional PMd activation reflects solely the formation of a new node with direct uncrossed projections to the spinal cord via the anterior CST. Instead, for these patients the contralesional PMd may become an important node in a cortico–cortical network (Dum and Strick 2005; Wise 1985), with functional connectivity to paretic limb alpha motoneurons via transcallosal pathways to the ipsilesional M1 (Bestmann et al. 2010; Grefkes et al. 2008).

The motor network has dense interhemispheric connectivity via the corpus callosum connecting premotor, motor and parietal nodes through cortico–cortical pathways (Strens et al. 2004). Disruption of these pathways can lead to specific deficits in motor planning or execution depending on the nodes affected. Re-organisation along these pathways can shape recovery. The connectivity between nodes can be assessed in the resting state or during motor tasks after stroke, and compared to healthy adults. After stroke there is evidence of disturbed neural activity in regions distant to the lesion which impacts on motor function (Alstott et al. 2009; Seitz et al. 1999) and the extent of network disturbance has been shown to correlate with impairment level and upper limb recovery (Grefkes et al. 2008). For example, the predominant functional influence of each M1 on the other is mutual inhibition, a phenomenon readily demonstrated using dual-coil TMS, and found to be disrupted after stroke (Murase et al. 2004; Shimizu et al. 2002). The disruption of mutual inhibition between the left and right M1, assessed with TMS, relates to upper limb impairment (Murase et al. 2004) and its restoration with recovery of function (Stinear et al. 2008). Similarly, disruptions in functional connectivity between ipsilesional and contralesional nodes of the motor network have been assessed using fMRI and dynamic causal modelling (DCM), to identify temporally correlated activity across network nodes from measures of effective connectivity. The advantage of whole-brain fMRI over dual-coil TMS is that a larger number of network nodes can be examined simultaneously. Interestingly, however, the predominant and consistent finding from fMRI and DCM analyses is also that of disrupted mutual M1 inhibition after stroke. Reduced facilitation between ipsilesional M1 and SMA, and a de-coupling of contralesional SMA, has also been observed in chronic subcortical stroke patients with upper limb weakness (Grefkes et al. 2008).

The number of longitudinal studies examining network level dynamics after stroke is limited. Using fMRI has shown that neural activity associated with affected hand movement tends to increase bilaterally in the initial months after stroke, perhaps indicative of immediate disinhibition and reorganisation, followed by consolidation of a new network for task performance (Ward et al. 2003). At the time of the study, dynamic causal modelling approaches were not in use and a causal relationship between nodes could not be determined. More recently, Rehme and co-workers used DCM to examine network dynamics in 12 patients with subcortical lesions and upper limb impairment within 72 h, and 1–2 weeks post-stroke (Rehme et al. 2011b) and then 3–6 months later at the early chronic stage (Rehme et al. 2011a). In brief, patients performed an fMRI task requiring opening and closing of the paretic hand. Changes in effective connectivity were correlated with recovery maps using DCM analyses. The results indicated an increase in positive coupling between ipsilesional premotor areas and M1 at the acute stage compared to healthy controls, followed by a decrease in functional connectivity between these areas after 3 months. Patients who maintained abnormal inhibitory coupling between the contralesional and ipsilesional M1 tend to have greater impairment after 3 months. A potential limitation of these studies was a lack of control over mirror activity in the unaffected hand to ensure contralesional activation (or coupling to contralesional areas) was correctly ascribed to affected hand control. This is a common limitation of fMRI studies of manual performance that do not monitor hand EMG and kinematics bilaterally. Conversely, studies which demonstrate parametric modulation of the BOLD signal with task performance are probably better suited to eliminating this potential bias (Ward et al. 2007). The generalisability of the results from Rehme and colleagues is limited, because the majority of patients scored near maximum on the Action Research Arm Test at the acute stage. Therefore, recovery profiles were limited by ceiling effects, and based on a very small number of patients with moderate or severe initial impairment. Even so, the studies by Rehme and colleagues provide an indication of early versus late changes in motor network function after stroke resulting in upper limb weakness, which overall seem biased toward ipsilesional network activity in patients who make a good recovery, and perhaps inevitably, a strengthened bilateral network for affected upper limb control in patients with greater impairment. Importantly, these findings indicate that beyond a certain level of impairment, there will be no functional advantage gained by suppression of nodes within the contralesional hemisphere. This has implications for the use of non-invasive brain stimulation (NIBS) in conjunction with rehabilitation.

13.2.3 Brain Stimulation to Modify Connectivity

In the past decade, there have been several relatively small-scale studies that have examined the efficacy of NIBS for assisting motor recovery after stroke (for recent review see Hummel et al. 2008). The premise for the use of NIBS after stroke is

based on the interhemispheric competition model. For example, NIBS might facilitate motor recovery by increasing the excitability of neurons within the ipsilesional hemisphere, such as surviving ipsilesional corticospinal neurons mainly in M1, to maximise the extent of ipsilesional cortical control over the paretic side via the lateral CST. The second approach is to reduce excitability of the contralesional M1 using suppressive NIBS, in an attempt to restore balanced excitability between the hemispheres. In this model, it is thought that hypo-excitability of ipsilesional M1 may result, at least in part, from increased tonic inhibition in perilesional neurons (Donoghue et al. 1990). The ipsilesional M1 then exerts less inhibition via the corpus callosum to the contralesional M1 (Shimizu et al. 2002). This may account for the hyperexcitability of contralesional M1, which in turn exerts a greater inhibitory influence over the ipsilesional M1 (Murase et al. 2004). This tonic inhibitory drive acting on ipsilesional M1 may impede neural plasticity and reorganisation (Clarkson et al. 2010). This positive feedback cycle leads to a persistent imbalance in hemispheric excitability and is associated with poor motor outcomes (Traversa et al. 1998). Therefore, NIBS may be used to break down this cycle and facilitate hemispheric re-balancing (Hummel and Cohen 2006).

The most common approach has been to examine the effects of NIBS on brain activation, motor cortex excitability and motor function in single-session studies. Kim and colleagues found that for 15 chronic patients with upper limb weakness after stroke, a single application of 10 Hz rTMS to ipsilesional M1 increased the size of MEPs elicited in a paretic hand muscle, presumably due to an increase in ipsilesional M1 excitability. The patients' accuracy on a sequential motor learning task also improved. Importantly, the extent of facilitation in paretic side MEPs after rTMS positively correlated with improvements in task performance. Similarly, anodal transcranial direct current stimulation (a-tDCS) of the ipsilesional M1 increases its excitability and improves paretic hand function in a correlated manner for patients at the chronic stage after subcortical stroke (Hummel et al. 2005). In this study, there was an accompanying decrease in ipsilesional M1 intracortical inhibition after a-tDCS. This reduction of presumed GABAergic inhibition is an indication that a-tDCS might enhance LTP-like plasticity through disinhibition, perhaps unmasking functional pathways with latent synapses to intact descending CST or cortico-reticulo-spinal neurons. Therefore, ipsilesional NIBS that enhances excitability through reduced inhibition may result in the functional integration of a new ipsilesional cortical node that can produce descending output to alpha motoneurons, at least in well-recovered patients.

There have been several studies that have applied 1 Hz rTMS to the contralesional M1 in an attempt to improve motor function of the paretic limb (for example, Dafotakis et al. 2008; Khedr et al. 2009; Takeuchi et al. 2005). Takeuchi and colleagues applied 1 Hz or sham rTMS to contralesional M1 in 20 chronic subcortical stroke patients and examined paretic hand function, M1 excitability and interhemispheric inhibition (IHI). Paretic hand function improved after contralesional M1 rTMS and improvements scaled with a decrease in IHI between the contralesional and ipsilesional M1 (Takeuchi et al. 2005). This shows that NIBS applied to the contralesional M1 can reduce the abnormally high IHI acting on ipsilesional M1 observed after stroke (Murase et al. 2004).

There has been recent interest in the use of patterned rTMS in the form of theta burst stimulation (TBS) to facilitate motor recovery after stroke (Ackerley et al. 2010; Di Lazzaro et al. 2008, 2010; Talelli et al. 2007a). TBS of human motor cortex typically involves delivering bursts of three stimuli separated by 20 ms with an inter-burst frequency of 5 Hz (theta). Delivered intermittently (iTBS) in 2 s trains with an 8 s inter-train interval, 300–600 stimuli produce facilitatory effects on M1 which outlast the stimulation period. Conversely, bursts delivered continuously (cTBS) can suppress M1 excitability, at least in healthy participants (Huang et al. 2005, but see also Gentner et al. 2008). At the acute stage the excitability of ipsilesional M1 can be facilitated by both iTBS of the ipsilesional M1 and cTBS of the contralesional M1 (Di Lazzaro et al. 2008). In patients at the chronic stage, iTBS of ipsilesional M1 increased excitability and improved reaction time of the paretic hand, whereas cTBS had a suppressive effect when applied to contralesional M1 but did not affect behaviour (Talelli et al. 2007b). TBS has also been combined with upper limb therapy to determine if it facilitates the behavioural effects (Ackerley et al. 2010). Intermittent TBS had the expected effect of increasing ipsilesional M1 excitability and improving measures of paretic hand precision grip, compared to sham stimulation. Interestingly, cTBS of contralesional M1 produced an unexpected decrease in ipsilesional M1 excitability, presumably through interhemispheric pathways, although these were not examined directly. Across the group, the decrease in ipsilesional M1 excitability after contralesional cTBS correlated with a decrement in upper limb function during the session. These results indicate that the effects of iTBS, like those of a-tDCS, may be robust and predictable when applied in the context of voluntary motor training, whereas the neurophysiological aftereffects induced by cTBS may interact with voluntary activity in unpredictable or undesirable ways.

The examples above demonstrate local and remote effects of NIBS on either M1, assessed with TMS, and how these effects relate to motor function. Another approach is to use NIBS to explore altered connectivity across a wider network of brain areas in relation to motor function after stroke. In a concurrent rTMS-fMRI study, Bestmann and colleagues examined state-dependent interactions between remote, but interconnected regions across the brains of 12 chronic patients with upper limb impairment (Bestmann et al. 2010). High or low intensity rTMS (5 pulses at 11 Hz) was delivered to contralesional PMd during a paced isometric hand grip task performed with the affected hand. In a separate experiment, functional connectivity between contralesional PMd and ipsilesional M1 was assessed with dual-coil TMS. The fMRI data indicated that activation peaks in ipsilesional and contralesional PMd and SMA increased after high-intensity compared to low-intensity rTMS during affected hand grip. Importantly, the extent of increase in contralesional activation scaled negatively with paretic upper limb function as observed previously (Ward et al. 2007). Not surprisingly, those patients with larger activation peaks in ipsilesional M1 had better function. Patients with worse function tended to have smaller and posteriorly shifted peaks in ipsilesional M1 activation. The dual-coil TMS study indicated that patients with better function maintained inhibition between contralesional PMd and ipsilesional M1, akin to

healthy adults (Mochizuki et al. 2004), but patients with worse function tended to show facilitation between these nodes. Interestingly, the extent of activation in this novel interhemispheric network identified with concurrent TMS and fMRI positively correlated to the extent of contralesional PMd—ipsilesional M1 facilitation obtained from dual-coil TMS in the same patients. In other words, patients with worse function tend to rely upon facilitatory inputs between contralesional PMd and ipsilesional M1 to a greater extent, whereas patients with better function maintain a more normal inhibitory network between these two nodes.

In a similar study, 11 sub-acute patients with mild upper limb impairment were scanned 1−3 months after stroke while performing paretic hand closure, and DCM analysis of effective connectivity was performed (Grefkes et al. 2010). Suppressive rTMS of contralesional M1 significantly improved the motor function of the paretic hand. The connectivity analysis revealed that the behavioural improvements in response to rTMS correlated with a reduction of the suppressive influences of contralesional M1 on ipsilesional M1 during paretic hand movements. Concurrently, connectivity between ipsilesional SMA and M1 increased after contralesional M1 1 Hz rTMS. The results suggest that rTMS of contralesional M1 can produce both a reduction of maladaptive transcallosal inhibitory influences (originating from contralesional M1) and a restitution of ipsilesional effective connectivity between SMA and M1. For patients with mild impairments, this may lead to improved motor function of the paretic hand , but this would need to be tested with repeated applications and by using clinical assessments of function.

Remote effects of NIBS across multiple sessions have not been investigated widely. In a sham controlled study of 52 sub-acute stroke patients, Khedr and colleagues found that 10 daily applications of 3 Hz rTMS to ipsilesional M1 led to less disability in patients at 3 months post-stroke (Khedr et al. 2005). The suggestion was that rTMS may have facilitated M1 plasticity in response to physical therapy, however, ipsilesional M1 excitability did not change after the intervention, and remote effects on cortical excitability were not assessed. In a later study (Khedr et al. 2009), the effects of 1 Hz rTMS of contralesional M1 and 3 Hz rTMS of ipsilesional M1 were compared in 36 patients treated over 5 consecutive days. Interestingly, contralesional M1 1 Hz rTMS caused local and remote effects producing more balanced M1 excitability across both hemispheres, whereas 3 Hz rTMS of ipsilesional M1 increased its excitability without changing contralesional M1 excitability. Patients who received suppressive rTMS of contralesional M1 had better outcomes at 3 months than patients who received facilitatory rTMS of ipsilesional M1, or sham stimulation. A similar finding was reported in patients at the chronic stage after five daily sessions of 1 Hz rTMS (or sham) was applied to contralesional M1. The protocol promoted more balanced M1 excitability across hemispheres, with a remote increase in ipsilesional M1 excitability that correlated with improvement in a reaction time task performed with the paretic hand (Fregni et al. 2006). Recently, bi-hemispheric tDCS plus upper limb therapy was shown to produce greater improvements than therapy alone, in 15 chronic patients with upper limb impairment (Lindenberg et al. 2011). Interestingly, the extent of functional improvements after tDCS-assisted therapy scaled positively with

ipsilesional CST integrity as observed previously (Lindenberg et al. 2009; Stinear et al. 2007), as well as with the integrity of M1–M1 corpus callosum pathways (Lindenberg et al. 2011).

Overall these results indicate that non-invasive stimulation of a cortical target applied once, or over a number of sessions, alters excitability of the target node, as well as other network nodes distant from the site of stimulation. For the motor system, remote effects are mainly seen in the opposite M1 and premotor areas including SMA. Generally, approaches that produce more balanced excitability across the primary motor cortices tend to produce more favourable outcomes, but the caveat is that patients with greater levels of impairment rely more heavily on contralesional cortical areas (perhaps PMd in particular). It is worth remembering that down-regulation of contralesional M1 excitability with NIBS after stroke may be advantageous for well-recovered patients (Grefkes et al. 2008), but contraindicated for more impaired patients (Ackerley et al. 2010; Bradnam et al. 2011). The target of NIBS and its functional connections to remote nodes in the motor network needs to be considered carefully, perhaps especially when considering suppressive NIBS to contralesional nodes.

13.3 Language System

13.3.1 Ipsilesional Connectivity

Stroke lesions affecting the left frontal and temporal cortices, and adjacent white matter, can impair language function. In general, speech production is impaired by lesions affecting the inferior frontal gyrus (Broca's area), speech comprehension is impaired by lesions affecting the posterior temporal lobe (Wernicke's area), and speech repetition is impaired by lesions affecting white matter tracts connecting these two cortical nodes (arcuate fasciculus and superior longitudinal fasciculus) (Kreisler et al. 2000).

The importance of preserved left hemisphere language nodes and perilesional cortex for the recovery of language function has been demonstrated by a number of neuroimaging studies (Crinion and Leff 2007; Fridriksson 2010; Meinzer et al. 2008; Menke et al. 2009). Suppressing left IFG activity with rTMS impairs language function in most patients at the sub-acute stage, confirming its essential role in the language network (Winhuisen et al. 2005).

The integration of left hemisphere nodes outside the 'classical' language network is also commonly observed (Turkeltaub et al. 2011), and may be a result of intrahemispheric collateral disinhibition (Heiss and Thiel 2006). For example, better naming performance is linearly related to greater activity in left middle frontal and inferior occipital gyri in chronic stroke patients (Fridriksson et al. 2010). These areas are in close proximity, but not strictly within, the 'classical' frontal and temporal language nodes, and their increased activity during naming

may reflect expansion of these functional nodes into preserved cortex. However, this ipsilesional reorganisation may not always support better function. When patients with chronic receptive aphasia perform a spoken word memory task, they exhibit significantly less left superior temporal gyrus (STG) activation compared to control subjects. As might be expected, greater impairment is related to less left STG activity (Breier et al. 2004). Interestingly, impairment may also be greater in patients with more activity at other ipsilesional sites, such as adjacent middle and inferior temporal gyri, indicating that the recruitment of ipsilesional nodes of the language network may reflect incomplete compensation (Breier et al. 2004) or a non-compensatory remote disturbance in language network activity.

Lesions affecting the left arcuate fasciculus (AF) and superior longitudinal fasciculus reduce the functional connectivity between the frontal and temporal cortices (Breier et al. 2008). Traditionally, this is thought to produce conduction aphasia, characterised by impaired speech repetition (Kreisler et al. 2000). Alternatively, the AF may form an important functional connection for motor elements of speech production, by connecting the temporal lobe and pars opercularis via the ventral premotor cortex (Kaplan et al. 2010). Impairment due to stroke affecting the AF may therefore reflect a deficit in speech motor planning and sequencing, rather than a deficit in language comprehension or production (Bernal and Ardila 2009), highlighting the importance of pathways that link the language and motor networks.

13.3.2 Contralesional and Interhemispheric Connectivity

The cortical network for language function is bilaterally distributed across the frontal and temporal lobes. Typically, the activity in this network is strongly lateralised to the left hemisphere (Kreisler et al. 2000), which is thought to suppress the activity in homotopic right hemisphere nodes via inhibitory transcallosal connections (Hamilton et al. 2011; Thiel et al. 2006). After stroke affecting the left hemisphere language network, the suppression of right hemisphere homologues is thought to be lifted, possibly allowing their latent capacity for language processing to contribute to recovery of function (Andoh and Martinot 2008). There is convincing evidence that right hemisphere nodes are activated during language tasks after stroke, in addition to preserved left hemisphere nodes (Hamilton et al. 2011; Turkeltaub et al. 2011). Furthermore, right hemisphere fronto-temporal sites are connected by white matter pathways homologous to those in the left hemisphere (Kaplan et al. 2010), supporting the idea that the recruitment of right hemisphere nodes contributes to recovery of function. However, this idea continues to be debated (Meinzer et al. 2011).

The evolution of language network activity over the weeks and months following stroke is similar to that observed for motor network activity. Longitudinal functional imaging has shown that at the acute stage, language network activity is markedly suppressed bilaterally during attempted language tasks in patients with aphasia (Saur et al. 2006). At this stage, greater left IFG function is associated

with better language function, as might be expected. Upregulation of bilateral network activity is observed at the sub-acute stage, particularly at the Broca's area homologue in the right IFG. The extent of activation at this node is related to the degree of improvement in language function during the sub-acute stage (Saur et al. 2006). Disruption of right IFG activity with repetitive TMS impairs language function in patients with less left IFG activity at this stage of recovery (Winhuisen et al. 2005). These findings, and those of other studies, indicate that up-regulation of right hemisphere nodes may play a limited compensatory role in the recovery of language function (Heiss and Thiel 2006).

At the chronic stage, better recovery is associated with a reversion to left lateralised network activity (Saur et al. 2006; van Oers et al. 2010), though persistent right IFG activity does not preclude recovery of function (Winhuisen et al. 2007). Improvements in speech production are associated with increased structural connectivity between right language nodes in more severely impaired patients who receive therapy aimed at facilitating right hemisphere cortical activity (Schlaug et al. 2009). The functional connectivity between motor and language networks is also altered at the chronic stage. For example, left M1 excitability is reduced when healthy adults read aloud, but not when they make meaningless sounds. This effect is observed in the right hemisphere of chronic aphasia patients, which supports the idea that right hemisphere language nodes become more functionally integrated in the language network after stroke (Meister et al. 2006). Increased functional connectivity between left and right anterolateral superior temporal cortex is also related to better auditory word and sentence comprehension in stroke patients with receptive aphasia at the chronic stage (Warren and Crinion 2009). However, patients' positive response to constraint-induced language therapy is only temporary if they have initially high levels of right hemisphere language activity (Breier et al. 2009). Together, these studies indicate that a greater contribution of right hemisphere nodes to language network activity may play a role in improving language function after stroke. However, these improvements are likely to be temporary or incomplete, and reintegration of left hemisphere nodes is an essential feature of favourable recovery (Heiss and Thiel 2006).

An alternative theory is that increased activity in right hemisphere nodes may be maladaptive, possibly disturbing language network activity by suppressing left hemisphere nodes via inhibitory transcallosal connections. For example, there is some evidence that naming errors are specifically related to activity in right IFG in chronic aphasia patients (Postman-Caucheteux et al. 2010), though this activity may reflect non-linguistic cognitive processing rather than a maladaptive response (van Oers et al. 2010).

13.3.3 Brain Stimulation to Modify Connectivity

Given the clear evidence of the left hemisphere's essential role in recovery of language function, applying facilitatory brain stimulation to left hemisphere

language nodes may be a useful adjunct to speech language therapy. The potential benefits of applying facilitatory or suppressive brain stimulation to right hemisphere language nodes are less predictable, and may depend on the extent of impairment and stage of recovery.

Single applications of repetitive TMS to language network nodes have shed light on their roles in language function after stroke, as described in previous sections. Repeated applications, with or without concomitant speech language therapy, may produce long-term benefits. Ten daily applications of facilitatory rTMS to left IFG have been shown to improve fluency in a small group of patients at the chronic stage of stroke fMRI (Szaflarski et al. 2011). These behavioural effects were accompanied by a leftward shift in language network activity, detected with fMRI. While these results are promising, there was no control group or sham stimulation condition, so further investigation is required. Facilitatory a-tDCS of left IFG (Baker et al. 2010) and perilesional cortex (Fridriksson et al. 2011) has been found to improve naming accuracy and speed respectively in chronic stroke patients. In these sham-controlled studies, patients received five daily applications of a-tDCS while they undertook computer-based naming therapy. The benefits were maintained for at least 1 (Baker et al. 2010) and 3 weeks (Fridriksson et al. 2011).

Repetitive TMS has also been used to suppress activity in right hemisphere language nodes. Chronic stroke patients experienced a greater improvement in language function after 10 daily speech language therapy sessions, when each session is preceded by suppressive rTMS of right IFG, compared to sham rTMS (Weiduschat et al. 2011). Furthermore, patients who received sham rTMS and therapy exhibited a rightward shift in IFG activity, detected by PET, which was not observed in patients who received suppressive rTMS of this site. These results indicate that suppressive rTMS may reduce the recruitment of right hemisphere language nodes, and this may be associated with a better response to therapy, however, no specific correlation was found (Weiduschat et al. 2011). Similar studies have found the benefits of suppressive rTMS of right IFG can be maintained for at least 2 months (Barwood et al. 2011; Naeser et al. 2005).

Suppressive cathodal tDCS of right IFG, delivered in five daily sessions during word retrieval therapy, has been shown to improve picture naming, compared to therapy combined with sham stimulation (Kang et al. 2011). Cathodal tDCS of right STG, delivered in 10 daily sessions during speech language therapy, has also been found to improve auditory verbal comprehension to a greater extent than a-tDCS or sham stimulation of left STG, in patients at the sub-acute stage of recovery (You et al. 2011). Unfortunately, neither of these studies included a follow-up evaluation to determine whether these benefits were sustained.

These studies indicate that facilitating left hemisphere activity, or suppressing right hemisphere activity, with NIBS during speech language therapy might be beneficial. This fits with the interhemispheric competition model (Andoh and Martinot 2008). However, the few studies conducted in this area are often limited by small sample sizes, no sham control, and short follow-up periods. Further work is required to address these limitations, and to optimise protocols for individual patients. For example, if the right hemisphere plays an important role in language

recovery at the sub-acute stage (Crinion and Leff 2007; Saur et al. 2006), suppressing its activity at this stage may be deleterious. While You et al. (2011) observed an immediate benefit of suppressing right STG in sub-acute patients, the long-term effects are unknown.

13.4 Spatial Attention System

13.4.1 Ipsilesional Connectivity

Spatial neglect refers to the failure to detect, attend or respond to stimuli contralateral to a brain lesion, most commonly of the right hemisphere (Bartolomeo 2007; Corbetta and Shulman 2011). The neural mechanisms of attention, and their functional lateralisation, are the subject of ongoing debate (Doricchi 2008). One theory is that the predominance of right hemisphere lesions in patients with neglect reflects differences in the lateralisation of the dorsal and ventral attention networks. The dorsal network is involved in spatial attention and voluntary visuomotor behaviour through the top-down selection of salient stimuli on the basis of goals, and is thought to be bilaterally distributed. In contrast, the ventral network contributes to vigilance and re-orients attention to detected stimuli, particularly when they are unexpected or behaviourally relevant. The ventral network is thought to be right lateralised, and to provide excitatory input to the dorsal network that triggers a shift in attention (Corbetta and Shulman 2002). Lesion mapping has shown that stroke patients with spatial neglect typically have lesions affecting right frontal, parietal and temporal cortices and insular cortex. A more detailed factorial analysis has revealed that damage to each of these nodes is associated with specific components of the spatial neglect syndrome. Right inferior parietal lobe lesions are related to visuospatial neglect; right dorsolateral prefrontal cortex lesions are related to impaired exploratory behaviour and visuomotor neglect; and right temporal lobe lesions are related to object-centred neglect (Verdon et al. 2010). Neglect can also result from damage to white matter pathways such as the inferior and superior occipitofrontal and superior longitudinal fasciculi, resulting in disconnection of frontal and parietal nodes (Bartolomeo et al. 2007; Karnath et al. 2009; Urbanski 2011). Stroke lesions, affecting ventral right hemisphere nodes and white matter pathways, can both directly affect the ventral attention network, and indirectly impair processing in the dorsal attention network (Corbetta and Shulman 2011).

Evidence in support of this model comes from fMRI studies, showing that at the acute stage after stroke, patients with neglect exhibit markedly reduced right dorsal posterior parietal and dorsolateral prefrontal cortex activity during a visual orienting task, even if these nodes are intact (Corbetta et al. 2005). This is thought to occur due to a lack of excitatory input to the dorsal network from the lesioned ventral network, possibly via the right middle frontal gyrus (MFG) which appears to be a shared node that links the ventral and dorsal attention networks (He et al. 2007). Functional connectivity between right MFG and posterior intraparietal sulcus (pIPS), measured

with fMRI, is disrupted at the acute stage of stroke and the degree of disruption is related to the degree of impairment (He et al. 2007). The right frontal eye field (FEF) also provides crucial input to the posterior parietal cortex via the superior longitudinal fasciculus. When the right FEF and its posterior projections are intact, patients exhibit an attentional bias to task-relevant stimuli in ipsilesional space. In contrast, when this frontal node is disconnected from the dorsal posterior parietal node, patients exhibit an attentional bias to all stimuli in ipsilesional space, regardless of their relevance (Ptak and Schnider 2010). This indicates that the FEF in the dorsal attention network plays an important role in selecting which stimuli are attended to, on the basis of current goals.

Neurophysiological studies have confirmed the important role of the right parietal cortex in spatial attention in healthy adults (Sack 2010). For example, contralateral neglect of visual and tactile stimuli can be mimicked in healthy volunteers with single pulse (Fierro et al. 2001), paired pulse (Koch et al. 2005; Oliveri et al. 2000a) and repetitive TMS (Cazzoli et al. 2009; Fierro et al. 2000; Nyffeler et al. 2008) of right parietal cortex. Interestingly, rTMS of right parietal cortex also produces a rightward bias in the mental number line (Gobel et al. 2006), a phenomenon often observed in patients with right hemisphere lesions and spatial neglect. Contralateral neglect can also be mimicked with rTMS of right frontal cortex (Brighina et al. 2002), confirming the right lateralisation of the spatial attention network.

13.4.2 Contralesional and Interhemispheric Connectivity

The interhemispheric competition model is a prevailing theory for the functional connectivity between posterior parietal lobes (PPLs). This model proposes that the PPLs mutually inhibit each other, via transcallosal white matter connections. Stroke affecting either lobe can disrupt the balance of this mutual inhibition, resulting in relative contralesional overactivity. This model emphasises the role of the contralesional hemisphere in the resulting attentional imbalance, and is supported by studies that have used TMS to suppress parietal cortex activity in healthy adults (Sack 2010). For example, suppressive rTMS of right PPL improves detection of ipsilateral visual targets, suggesting a facilitation of activity in the left PPL, possibly due to suppression of interhemispheric inhibition from the stimulated right PPL (Hilgetag et al. 2001). Similarly, the detection of a visual target is impaired when contralateral parietal cortex is disrupted with single pulse TMS delivered 150 ms after target presentation. This effect is greater for right than left parietal disruption (Dambeck et al. 2006). Interestingly, simultaneous disruption of both parietal lobes had no net effect on target detection, presumably because the balance of interhemispheric inhibition between the stimulated nodes was unchanged (Dambeck et al. 2006).

Patients with neglect exhibit an imbalance in the activation of dorsal posterior parietal node activity during a visual orienting task, which evolves over the course of recovery. Activity in the right intra-parietal sulcus (IPS) and superior parietal lobule (SPL), measured with fMRI, is markedly reduced at the acute stage, and

increases with recovery. Conversely, activity in the homologous areas of the left hemisphere is increased at the acute stage, and decreases with recovery (Corbetta et al. 2005). This imbalance in cortical activity may be due to decreased functional connectivity between these parietal nodes (He et al. 2007), resulting in reduced right-to-left inhibition via transcallosal pathways. Furthermore, greater activity in the left parietal nodes and lower functional connectivity between the parietal nodes, are associated with greater impairment, particularly at the acute stage (Corbetta et al. 2005; He et al. 2007). Interestingly, the dorsal parietal nodes are the only ones to exhibit this imbalance, as activity in frontal nodes increases in both hemispheres during recovery (Corbetta et al. 2005) and reduced interhemispheric functional connectivity between other nodes of the dorsal attention network does not relate to the severity of visuospatial neglect (He et al. 2007).

Functional connectivity can also be assessed with TMS. Using two TMS coils, conditioning left posterior parietal cortex (PPC) 4 ms prior to stimulation of left M1 facilitates the amplitude of the resulting MEP recorded from the right hand, in healthy adults (Koch et al. 2007). This facilitatory effect is stronger in sub-acute stroke patients with visuospatial neglect than similar patients without neglect, or healthy adults. Furthermore, the degree of excessive PPC-M1 facilitation is positively related to the severity of visuospatial neglect symptoms (Koch et al. 2008). These findings extend the inter-hemispheric competition model, by providing a measure of functional connectivity between left hemisphere nodes that seems to reflect overactivity in the left hemisphere attention network.

Patients with right hemisphere stroke lesions can also exhibit extinction, where contralateral targets are not perceived when they are presented simultaneously with ipsilateral targets. Extinction of visual targets in the left hemifield can be mimicked in healthy adults with a single pulse of TMS delivered to right parietal cortex 150 ms after bilateral target presentation (Dambeck et al. 2006). In sub-acute stroke patients with right hemisphere lesions, extinction of tactile stimuli delivered to the left hand can be reduced by TMS of left hemisphere nodes of the attention network. Extinction is reduced by single and paired pulse TMS delivered to left frontal cortex 40 ms (Oliveri et al. 1999, 2000b) after bilateral tactile stimulation, and by paired pulse TMS of left parietal cortex 30 ms after bilateral tactile stimulation (Oliveri et al. 2000b). These studies support the interhemispheric competition model for extinction, in two sensory modalities, and underscore the distributed nature of the spatial attention network.

13.4.3 Brain Stimulation to Modify Connectivity

The dorsal attention network may be a better target for brain stimulation than the ventral attention network, which is more commonly damaged by stroke in patients with neglect. Furthermore, there is some evidence that functional connectivity in the lesioned ventral attention network remains disrupted at the chronic stage of recovery, even though visuospatial attention improves (He et al. 2007). This

indicates that the restoration of functional connectivity and rebalancing of cortical activity in the dorsal attention network, particularly the parietal nodes, is largely responsible for improvements in neglect symptoms. Brain stimulation protocols that promote rebalancing of cortical activity in the IPS and SPL, particularly at the sub-acute stage, may therefore have therapeutic benefit.

To date, most of the studies that have used NIBS to modify visuospatial attention network activity in stroke patients have been aimed at reducing activity in contralesional parietal cortex (Cazzoli et al. 2010). In sub-acute stroke patients, visuospatial neglect significantly improves after suppressive rTMS of left PPC delivered in 10 daily sessions, compared to a matched patient group (Song et al. 2009), and a sham control patient group (Koch et al. 2012). Suppressive rTMS of left PPC has also been found to normalise functional connectivity between left PPC and left M1 in sub-acute patients, by reducing the excitability of this facilitatory pathway (Koch et al. 2008). However, the observed improvements in visuospatial neglect were not related to these neurophysiological effects. Further work is needed to continue exploring this approach. In a sham-controlled study of 11 chronic stroke patients, the number of visual targets perceived in the left visual field improved after two applications of suppressive rTMS to the left parietal lobe, delivered 15 min apart. This beneficial effect was maintained for 8 h, and was extended to 32 h if four trains of stimuli were delivered on the same day (Nyffeler et al. 2009). These studies indicate that patients may benefit from rTMS protocols that decrease left parietal cortex activity, even at the chronic stage of recovery.

The effects of tDCS on visuospatial neglect have also been explored. In a sham-controlled study of 10 sub-acute stroke patients, both suppressive c-tDCS of left parietal cortex and facilitatory a-tDCS of right parietal cortex temporarily improved performance on a line bisection task. The degree of improvement after suppression of left parietal cortex was negatively related to lesion size (Sparing et al. 2009), indicating that over-activity in the contralesional attention network may be more functionally disabling in patients with greater damage to the right hemisphere attention network.

The potential benefits of combining therapy and brain stimulation have been explored in an open-label pilot study, comparing the outcomes with a control group who received therapy only (Lim et al. 2010). Line bisection performance tended to improve after 10 daily sessions of suppressive rTMS applied to the left parietal lobe immediately prior to 30 min of occupational therapy, relative to the comparison group (Lim et al. 2010). While these results are promising, further studies with sham control, and larger, more homogeneous patient groups, need to be conducted before any conclusions can be drawn.

13.5 Conclusions

Stroke produces motor, language and attention impairments via direct and remote effects on the networks responsible for these functions. Restoring these functions involves reorganisation of these networks, in terms of the activity of existing

nodes, the possible integration of new nodes, and changes in the functional connectivity between nodes. Rehabilitation can be viewed as an opportunity for the brain to find new patterns of activity that restore as much function as possible. However, the range of patterns available is limited by the anatomical connectivity between remaining nodes in the network, and potential new nodes. For example, it seems that damage to the CST is an important limiting factor in the motor system, as reorganisation of the cortical network cannot compensate for a loss of functional connectivity with the spinal cord.

The motor system is bilaterally lateralised, in that each side of the body is predominantly controlled by the opposite hemisphere. While the interhemispheric competition model predicts that suppressing contralesional activity is likely to be beneficial after stroke, this seems to be more likely if the ipsilesional M1 is still functionally connected to the spinal cord. With more damage to the ipsilesional CST, contralesional nodes may play an important compensatory role, via both cortico–cortical connections to ipsilesional nodes, and corticospinal connections to ipsilateral alpha motoneurons. Therefore, the choice of NIBS target and intended modulation of neural activity needs to be carefully considered, accounting for functional connectivity within the motor network of individual patients.

In contrast, the language and spatial attention systems are more strongly lateralised to one hemisphere. Stroke affecting the left hemisphere language network seems to result in disinhibition of contralesional nodes. Re-integration of ipsilesional nodes is essential for good recovery, though as for the motor system, persistent activity of the right hemisphere network does not preclude recovery. Stroke affecting the right hemisphere ventral attention network also results in disinhibition of contralesional nodes. Evidence of interhemispheric inhibition is perhaps clearest in the spatial attention system, and suppressive NIBS of contralesional nodes may have therapeutic benefit.

As we expand our understanding of the effects of stroke on these functional networks, we will move closer to the possibility of modifying activity and connectivity within these networks, with the aim of helping the brain to establish new patterns of activity that support the best possible recovery of function.

References

Ackerley SJ, Stinear CM, Barber PA, Byblow WD (2010) Combining theta burst stimulation with training after subcortical stroke. Stroke J Cereb Circ 41:1568–1572

Ahn YH, Ahn SH, Kim H, Hong JH, Jang SH (2006) Can stroke patients walk after complete lateral corticospinal tract injury of the affected hemisphere? NeuroReport 17:987–990

Alstott J, Breakspear M, Hagmann P, Cammoun L, Sporns O (2009) Modeling the impact of lesions in the human brain. PLoS Comput Biol 5:e1000408

Andoh J, Martinot JL (2008) Interhemispheric compensation: a hypothesis of TMS-induced effects on language-related areas. Eur Psychiatry 23:281–288

Baker JM, Rorden C, Fridriksson J (2010) Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke 41:1229–1236

Bartolomeo P (2007) Visual neglect. Curr Opin Neurol 20:381–386
Bartolomeo P, Thiebaut de Schotten M, Doricchi F (2007) Left unilateral neglect as a disconnection syndrome. Cereb Cortex 17:2479–2490
Barwood CH, Murdoch BE, Whelan BM, Lloyd D, Riek S, JD OS et al (2011) Improved language performance subsequent to low-frequency rTMS in patients with chronic non-fluent aphasia post-stroke. Eur J Neurol 18:935–943
Bernal B, Ardila A (2009) The role of the arcuate fasciculus in conduction aphasia. Brain 132:2309–2316
Bestmann S, Swayne O, Blankenburg F, Ruff CC, Teo J, Weiskopf N et al (2010) The role of contralesional dorsal premotor cortex after stroke as studied with concurrent TMS-fMRI. J Neurosci 30:11926–11937
Bradnam LV, Stinear CM, Barber PA, Byblow WD (2011) Contralesional hemisphere control of the proximal paretic upper limb following stroke. Cereb Cortex doi:10.1093
Breier JI, Castillo EM, Boake C, Billingsley R, Maher L, Francisco G et al (2004) Spatiotemporal patterns of language-specific brain activity in patients with chronic aphasia after stroke using magnetoencephalography. Neuroimage 23:1308–1316
Breier JI, Hasan KM, Zhang W, Men D, Papanicolaou AC (2008) Language dysfunction after stroke and damage to white matter tracts evaluated using diffusion tensor imaging. Am J Neuroradiol 29:483–487
Breier JI, Juranek J, Maher LM, Schmadeke S, Men D, Papanicolaou AC (2009) Behavioral and neurophysiologic response to therapy for chronic aphasia. Arch Phys Med Rehabil 90:2026–2033
Brighina F, Bisiach E, Piazza A, Oliveri M, La Bua V, Daniele O et al (2002) Perceptual and response bias in visuospatial neglect due to frontal and parietal repetitive transcranial magnetic stimulation in normal subjects. NeuroReport 13:2571–2575
Byrnes ML, Thickbroom GW, Phillips BA, Mastaglia FL (2001) Long-term changes in motor cortical organisation after recovery from subcortical stroke. Brain Res 889:278–287
Calautti C, Jones PS, Guincestre JY, Naccarato M, Sharma N, Day DJ et al (2010) The neural substrates of impaired finger tapping regularity after stroke. Neuroimage 50:1–6
Catano A, Houa M, Caroyer JM, Ducarne H, Noel P (1996) Magnetic transcranial stimulation in acute stroke: early excitation threshold and functional prognosis. Electroencephalogr Clin Neurophysiol 101:233–239
Cazzoli D, Muri RM, Hess CW, Nyffeler T (2009) Horizontal and vertical dimensions of visual extinction: a theta burst stimulation study. Neuroscience 164:1609–1614
Cazzoli D, Muri RM, Hess CW, Nyffeler T (2010) Treatment of hemispatial neglect by means of rTMS–a review. Restor Neurol Neurosci 28:499–510
Clarkson AN, Huang BS, Macisaac SE, Mody I, Carmichael ST (2010) Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. Nature 468:305–309
Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215
Corbetta M, Shulman GL (2011) Spatial neglect and attention networks. Annu Rev Neurosci 34:569–599
Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A (2005) Neural basis and recovery of spatial attention deficits in spatial neglect. Nat Neurosci 8:1603–1610
Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK et al (1997) A functional MRI study of subjects recovered from hemiparetic stroke. Stroke J Cereb Circ 28:2518–2527
Crinion JT, Leff AP (2007) Recovery and treatment of aphasia after stroke: functional imaging studies. Curr Opin Neurol 20:667–673
Dafotakis M, Grefkes C, Eickhoff SB, Karbe H, Fink GR, Nowak DA (2008) Effects of rTMS on grip force control following subcortical stroke. Exp Neurol 211:407–412
Dambeck N, Sparing R, Meister IG, Wienemann M, Weidemann J, Topper R et al (2006) Interhemispheric imbalance during visuospatial attention investigated by unilateral and bilateral TMS over human parietal cortices. Brain Res 1072:194–199
Davidoff RA (1990) The pyramidal tract. Neurology 40:332–339

Di Lazzaro V, Pilato F, Dileone M, Profice P, Capone F, Ranieri F et al (2008) Modulating cortical excitability in acute stroke: a repetitive TMS study. Clin Neurophysiol Off J Int Fed Clin Neurophysiol 119:715–723

Di Lazzaro V, Profice P, Pilato F, Capone F, Ranieri F, Pasqualetti P et al (2010) Motor cortex plasticity predicts recovery in acute stroke. Cereb Cortex 20:1523–1528

Donoghue JP, Suner S, Sanes JN (1990) Dynamic organization of primary motor cortex output to target muscles in adult rats. II. Rapid reorganization following motor nerve lesions. Experimental brain research. Experimentelle Hirnforschung. Exp Cereb 79:492–503

Doricchi F (2008) Thiebaut de Schotten M, Tomaiuolo F, Bartolomeo P. White matter (dis)connections and gray matter (dys)functions in visual neglect: gaining insights into the brain networks of spatial awareness. Cortex 44:983–995

Dum RP, Strick PL (1996) Spinal cord terminations of the medial wall motor areas in macaque monkeys. J Neurosci 16:6513–6525

Dum RP, Strick PL (2005) Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. J Neurosci 25:1375–1386

Duque J, Hummel F, Celnik P, Murase N, Mazzocchio R, Cohen LG (2005) Transcallosal inhibition in chronic subcortical stroke. Neuroimage 28:940–946

Fierro B, Brighina F, Oliveri M, Piazza A, La Bua V, Buffa D et al (2000) Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. NeuroReport 11:1519–1521

Fierro B, Brighina F, Piazza A, Oliveri M, Bisiach E (2001) Timing of right parietal and frontal cortex activity in visuo-spatial perception: a TMS study in normal individuals. NeuroReport 12:2605–2607

Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJ et al (2006) A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke 37:2115–2122

Fridriksson J (2010) Preservation and modulation of specific left hemisphere regions is vital for treated recovery from anomia in stroke. J Neurosci 30:11558–11564

Fridriksson J, Bonilha L, Baker JM, Moser D, Rorden C (2010) Activity in preserved left hemisphere regions predicts anomia severity in aphasia. Cereb Cortex 20:1013–1019

Fridriksson J, Richardson JD, Baker JM, Rorden C (2011) Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. Stroke 42:819–821

Gentner R, Wankerl K, Reinsberger C, Zeller D, Classen J (2008) Depression of human corticospinal excitability induced by magnetic theta-burst stimulation: evidence of rapid polarity-reversing metaplasticity. Cereb Cortex 18:2046–2053

Gerloff C, Bushara K, Sailer A, Wassermann EM, Chen R, Matsuoka T et al (2006) Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. Brain 129:791–808

Gobel SM, Calabria M, Farne A, Rossetti Y (2006) Parietal rTMS distorts the mental number line: simulating 'spatial' neglect in healthy subjects. Neuropsychologia 44:860–868

Grefkes C, Nowak DA, Eickhoff SB, Dafotakis M, Kust J, Karbe H et al (2008) Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. Ann Neurol 63:236–246

Grefkes C, Nowak DA, Wang LE, Dafotakis M, Eickhoff SB, Fink GR (2010) Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. Neuroimage 50:233–242

Hamilton RH, Chrysikou EG, Coslett B (2011) Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. Brain Lang 118:40–50

He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M (2007) Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. Neuron 53:905–918

Heald A, Bates D, Cartlidge NE, French JM, Miller S (1993) Longitudinal study of central motor conduction time following stroke. 2. Central motor conduction measured within 72 h after stroke as a predictor of functional outcome at 12 months. Brain J Neurol 116(Pt 6):1371–1385

Heiss WD, Thiel A (2006) A proposed regional hierarchy in recovery of post-stroke aphasia. Brain Lang 98:118–123

Hilgetag CC, Theoret H, Pascual-Leone A (2001) Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. Nat Neurosci 4:953–957

Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005) Theta burst stimulation of the human motor cortex. Neuron 45:201–206

Hummel FC, Cohen LG (2006) Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol 5:708–712

Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C et al (2005) Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain J Neurol 128:490–499

Hummel FC, Celnik P, Pascual-Leone A, Fregni F, Byblow WD, Buetefisch CM, et al (2008) Controversy: noninvasive and invasive cortical stimulation show efficacy in treating stroke patients. Brain Stimul 1:370–382

James GA, Lu ZL, VanMeter JW, Sathian K, Hu XP, Butler AJ (2009) Changes in resting state effective connectivity in the motor network following rehabilitation of upper extremity poststroke paresis. Top Stroke Rehabil 16:270–281

Jang SH (2009) The role of the corticospinal tract in motor recovery in patients with a stroke: a review. NeuroRehabilitation 24:285–290

Jankowska E, Edgley SA (2006) How can corticospinal tract neurons contribute to ipsilateral movements? A question with implications for recovery of motor functions. Neuroscientist 12:67–79

Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM (2002) The role of ipsilateral premotor cortex in hand movement after stroke. Proc Natl Acad Sci U S A 99:14518–14523

Kang EK, Kim YK, Sohn HM, Cohen LG, Paik NJ (2011) Improved picture naming in aphasia patients treated with cathodal tDCS to inhibit the right Broca's homologue area. Restor Neurol Neurosci 29:141–152

Kaplan E, Naeser MA, Martin PI, Ho M, Wang Y, Baker E et al (2010) Horizontal portion of arcuate fasciculus fibers track to pars opercularis, not pars triangularis, in right and left hemispheres: a DTI study. Neuroimage 52:436–444

Karnath HO, Rorden C, Ticini LF (2009) Damage to white matter fiber tracts in acute spatial neglect. Cereb Cortex 19:2331–2337

Khedr EM, Ahmed MA, Fathy N, Rothwell JC (2005) Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. Neurology 65:466–468

Khedr EM, Abdel-Fadeil MR, Farghali A, Qaid M (2009) Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. Eur J Neurol Off J Eur Fed Neurol Soc 16:1323–1330

Koch G, Oliveri M, Torriero S, Caltagirone C (2005) Modulation of excitatory and inhibitory circuits for visual awareness in the human right parietal cortex. Exp Brain Res 160:510–516

Koch G, Fernandez Del Olmo M, Cheeran B, Ruge D, Schippling S, Caltagirone C et al (2007) Focal stimulation of the posterior parietal cortex increases the excitability of the ipsilateral motor cortex. J Neurosci 27:6815–6822

Koch G, Oliveri M, Cheeran B, Ruge D, Lo Gerfo E, Salerno S, et al (2008) Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. Brain 131:3147–3155

Koch G, Bonni S, Giacobbe V, Bucchi G, Basile B, Lupo F et al (2012) Theta-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect. Neurology 78:24–30

Kreisler A, Godefroy O, Delmaire C, Debachy B, Leclercq M, Pruvo JP et al (2000) The anatomy of aphasia revisited. Neurology 54:1117–1123

Lim JY, Kang EK, Paik NJ (2010) Repetitive transcranial magnetic stimulation to hemispatial neglect in patients after stroke: an open-label pilot study. J Rehabil Med 42:447–452

Lindenberg R, Renga V, Zhu LL, Betzler F, Alsop D, Schlaug G (2009) Structural integrity of corticospinal motor fibers predicts motor impairment in chronic stroke. Neurology 74:280–287

Lindenberg R, Zhu LL, Ruber T, Schlaug G (2011) Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging. Hum Brain Mapp 33:1040–1051

Lotze M, Markert J, Sauseng P, Hoppe J, Plewnia C, Gerloff C (2006) The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. J Neurosci 26:6096–6102

Mackay J, Mensah G, Mendis S, Greenlund K (2004) The atlas of heart disease and stroke. World Health Organization, Geneva

Mazevet D, Meunier S, Pradat-Diehl P, Marchand-Pauvert V, Pierrot-Deseilligny E (2003) Changes in propriospinally mediated excitation of upper limb motoneurons in stroke patients. Brain 126:988–1000

Meinzer M, Flaisch T, Breitenstein C, Wienbruch C, Elbert T, Rockstroh B (2008) Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. Neuroimage 39:2038–2046

Meinzer M, Harnish S, Conway T, Crosson B (2011) Recent developments in functional and structural imaging of aphasia recovery after stroke. Aphasiology 25:271–290

Meister IG, Sparing R, Foltys H, Gebert D, Huber W, Topper R et al (2006) Functional connectivity between cortical hand motor and language areas during recovery from aphasia. J Neurol Sci 247:165–168

Menke R, Meinzer M, Kugel H, Deppe M, Baumgartner A, Schiffbauer H et al (2009) Imaging short- and long-term training success in chronic aphasia. BMC Neurosci 10:118

Mochizuki H, Huang YZ, Rothwell JC (2004) Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. J Physiol 561:331–338

Murase N, Duque J, Mazzocchio R, Cohen LG (2004) Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol 55:400–409

Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Kobayashi M et al (2005) Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. Brain Lang 93:95–105

Nowak DA, Grefkes C, Ameli M, Fink GR (2009) Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. Neurorehabil Neural Repair 23:641–656

Nudo RJ (2003) Adaptive plasticity in motor cortex: implications for rehabilitation after brain injury. J Rehabil Med 41S:7–10

Nyffeler T, Cazzoli D, Wurtz P, Luthi M, von Wartburg R, Chaves S et al (2008) Neglect-like visual exploration behaviour after theta burst transcranial magnetic stimulation of the right posterior parietal cortex. Eur J Neurosci 27:1809–1813

Nyffeler T, Cazzoli D, Hess CW, Muri RM (2009) One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. Stroke 40:2791–2796

Oliveri M, Rossini PM, Traversa R, Cicinelli P, Filippi MM, Pasqualetti P et al (1999) Left frontal transcranial magnetic stimulation reduces contralesional extinction in patients with unilateral right brain damage. Brain 122(Pt 9):1731–1739

Oliveri M, Caltagirone C, Filippi MM, Traversa R, Cicinelli P, Pasqualetti P et al (2000a) Paired transcranial magnetic stimulation protocols reveal a pattern of inhibition and facilitation in the human parietal cortex. J Physiol 529(Pt 2):461–468

Oliveri M, Rossini PM, Filippi MM, Traversa R, Cicinelli P, Palmieri MG et al (2000b) Time-dependent activation of parieto-frontal networks for directing attention to tactile space. A study with paired transcranial magnetic stimulation pulses in right-brain-damaged patients with extinction. Brain 123(Pt 9):1939–1947

O'Shea J, Johansen-Berg H, Trief D, Gobel S, Rushworth MF (2007) Functionally specific reorganization in human premotor cortex. Neuron 54:479–490

Pineiro R, Pendlebury S, Johansen-Berg H, Matthews PM (2001) Functional MRI detects posterior shifts in primary sensorimotor cortex activation after stroke: evidence of local adaptive reorganization? Stroke J Cereb Circ 32:1134–1139

Piron L, Piccione F, Tonin P, Dam M (2005) Clinical correlation between motor evoked potentials and gait recovery in poststroke patients. Arch Phys Med Rehabil 86:1874–1878

Postman-Caucheteux WA, Birn RM, Pursley RH, Butman JA, Solomon JM, Picchioni D et al (2010) Single-trial fMRI shows contralesional activity linked to overt naming errors in chronic aphasic patients. J Cogn Neurosci 22:1299–1318

Ptak R, Schnider A (2010) The dorsal attention network mediates orienting toward behaviorally relevant stimuli in spatial neglect. J Neurosci 30:12557–12565

Rehme AK, Eickhoff SB, Wang LE, Fink GR, Grefkes C (2011a) Dynamic causal modeling of cortical activity from the acute to the chronic stage after stroke. NeuroImage 55:1147–1158

Rehme AK, Fink GR, von Cramon DY, Grefkes C (2011b) The role of the contralesional motor cortex for motor recovery in the early days after stroke assessed with longitudinal FMRI. Cereb Cortex 21:756–768

Rossini PM, Caltagirone C, Castriota-Scanderbeg A, Cicinelli P, Del Gratta C, Demartin M et al (1998) Hand motor cortical area reorganization in stroke: a study with fMRI, MEG and TCS maps. Neuroreport 9:2141–2146

Sack AT (2010) Using non-invasive brain interference as a tool for mimicking spatial neglect in healthy volunteers. Restor Neurol Neurosci 28:485–497

Sanes JN, Donoghue JP (2000) Plasticity and primary motor cortex. Annu Rev Neurosci 23: 393–415

Saur D, Lange R, Baumgaertner A, Schraknepper V, Willmes K, Rijntjes M et al (2006) Dynamics of language reorganization after stroke. Brain 129:1371–1384

Schaechter JD, Fricker ZP, Perdue KL, Helmer KG, Vangel MG, Greve DN et al (2009) Microstructural status of ipsilesional and contralesional corticospinal tract correlates with motor skill in chronic stroke patients. Hum Brain Mapp 30:3461–3474

Schlaug G, Marchina S, Norton A (2009) Evidence for plasticity in white-matter tracts of patients with chronic Broca's aphasia undergoing intense intonation-based speech therapy. Ann N Y Acad Sci 1169:385–394

Schwerin S, Dewald JP, Haztl M, Jovanovich S, Nickeas M, MacKinnon C (2008) Ipsilateral versus contralateral cortical motor projections to a shoulder adductor in chronic hemiparetic stroke: implications for the expression of arm synergies. Exp Brain Res 185:509–519

Seitz RJ, Azari NP, Knorr U, Binkofski F, Herzog H, Freund HJ (1999) The role of diaschisis in stroke recovery. Stroke 30:1844–1850

Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB et al (2006) The lifetime risk of stroke: estimates from the Framingham Study. Stroke 37:345–350

Shimizu T, Hosaki A, Hino T, Sato M, Komori T, Hirai S et al (2002) Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke. Brain 125:1896–1907

Song W, Du B, Xu Q, Hu J, Wang M, Luo Y (2009) Low-frequency transcranial magnetic stimulation for visual spatial neglect: a pilot study. J Rehabil Med 41:162–165

Sparing R, Thimm M, Hesse MD, Kust J, Karbe H, Fink GR (2009) Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. Brain 132:3011–3020

Stinear C (2010) Prediction of recovery of motor function after stroke. Lancet Neurol 9: 1228–1232

Stinear JW, Byblow WD (2004) The contribution of cervical propriospinal premotoneurons in recovering hemiparetic stroke patients. J Clin Neurophysiol 21:426–434

Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD (2007) Functional potential in chronic stroke patients depends on corticospinal tract integrity. Brain 130: 170–180

Stinear CM, Barber PA, Coxon JP, Fleming MK, Byblow WD (2008) Priming the motor system enhances the effects of upper limb therapy in chronic stroke. Brain 131:1381–1390

Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD (2012) The PREP algorithm predicts potential for upper limb recovery after stroke. Brain 135:2427–2535

Strens LH, Asselman P, Pogosyan A, Loukas C, Thompson AJ, Brown P (2004) Corticocortical coupling in chronic stroke: its relevance to recovery. Neurology 63:475–484

Swayne OB, Rothwell JC, Ward NS, Greenwood RJ (2008) Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. Cereb Cortex 18:1909–1922

Szaflarski JP, Vannest J, Wu SW, DiFrancesco MW, Banks C, Gilbert DL (2011) Excitatory repetitive transcranial magnetic stimulation induces improvements in chronic post-stroke aphasia. Med Sci Monit 17:CR132–CR139

Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K (2005) Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke 36:2681–2686

Talelli P, Greenwood RJ, Rothwell JC (2007a) Exploring Theta Burst Stimulation as an intervention to improve motor recovery in chronic stroke. Clin Neurophysiol Off J Int Fed Clin Neurophysiol 118:333–342

Talelli P, Greenwood RJ, Rothwell JC (2007b) Exploring Theta Burst Stimulation as an intervention to improve motor recovery in chronic stroke. Clin Neurophysiol 118:333–342

Thiel A, Schumacher B, Wienhard K, Gairing S, Kracht LW, Wagner R et al (2006) Direct demonstration of transcallosal disinhibition in language networks. J Cereb Blood Flow Metab 26:1122–1127

Traversa R, Cicinelli P, Pasqualetti P, Filippi M, Rossini PM (1998) Follow-up on interhemispheric differences of motor evoked potentials from the "affected" and "unaffected" hemispheres in human stroke. Brain Res 803:1–8

Trompetto C, Assini A, Buccolieri A, Marchese R, Abbruzzese G (2000) Motor recovery following stroke: a transcranial magnetic stimulation study. Clin Neurophysiol Off J Int Fed Clin Neurophysiol 111:1860–1867

Turkeltaub PE, Messing S, Norise C, Hamilton RH (2011) Are networks for residual language function and recovery consistent across aphasic patients? Neurology 76:1726–1734

Turton A, Wroe S, Trepte N, Fraser C, Lemon RN (1996) Contralateral and ipsilateral EMG responses to transcranial magnetic stimulation during recovery of arm and hand function after stroke. Electroencephalogr Clin Neurophysiol 101:316–328

Urbanski M, Thiebaut de Schotten M, Rodrigo S, Oppenheim C, Touze E, Meder JF, et al (2011) DTI-MR tractography of white matter damage in stroke patients with neglect. Exp Brain Res 208:491–505

van Oers CA, Vink M, van Zandvoort MJ, van der Worp HB, de Haan EH, Kappelle LJ et al (2010) Contribution of the left and right inferior frontal gyrus in recovery from aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness. Neuroimage 49:885–893

Verdon V, Schwartz S, Lovblad KO, Hauert CA, Vuilleumier P (2010) Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. Brain 133:880–894

Ward NS, Brown MM, Thompson AJ, Frackowiak RS (2003) Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain 126:2476–2496

Ward NS, Newton JM, Swayne OB, Lee L, Thompson AJ, Greenwood RJ et al (2006) Motor system activation after subcortical stroke depends on corticospinal system integrity. Brain 129:809–819

Ward NS, Newton JM, Swayne OB, Lee L, Frackowiak RS, Thompson AJ et al (2007) The relationship between brain activity and peak grip force is modulated by corticospinal system integrity after subcortical stroke. Eur J Neurosci 25:1865–1873

Warren JE, Crinion JT, Lambon Ralph MA, Wise RJ (2009) Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. Brain 132:3428–3442

Weiduschat N, Thiel A, Rubi-Fessen I, Hartmann A, Kessler J, Merl P et al (2011) Effects of repetitive transcranial magnetic stimulation in aphasic stroke: a randomized controlled pilot study. Stroke 42:409–415

Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF et al (2005) Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. Stroke 36:1759–1763

Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF et al (2007) The right inferior frontal gyrus and poststroke aphasia: a follow-up investigation. Stroke 38:1286–1292

Wise SP (1985) The oprimate premtor cortex: past, present, and preparatory. Annu Rev Neurosci 8:1–19

Yao J, Chen A, Carmona C, Dewald JP (2009) Cortical overlap of joint representations contributes to the loss of independent joint control following stroke. NeuroImage 45:490–499

You DS, Kim DY, Chun MH, Jung SE, Park SJ (2011) Cathodal transcranial direct current stimulation of the right Wernicke's area improves comprehension in subacute stroke patients. Brain Lang 119:1–5

Chapter 14
Multiple Sclerosis

Mathias Wahl

Abstract Changes of connectivity and function occur at all stages and in all phenotypes of Multiple Sclerosis. In the early phase of the disease, these changes may remain clinically occult and undetectable by conventional MRI and established electrophysiologic methods. Connectivity in the MS brain can be assessed by modern neuroimaging techniques such as Diffusion Tensor Imaging and functional MRI as well as by neurophysiologic tools, namely Electroencephalography, Magnetoencephalography, and paired-coil Transcranial Magnetic Stimulation. These techniques allow quantitative assessment of anatomic connectivity, functional connectivity, and effective connectivity. Abnormalities revealed in the brains of patients with MS by these techniques include decreased regional white matter connectivity as well as task-related functional changes, namely overactivation of areas normally recruited by healthy individuals, increased and decreased connectivity between these areas, and recruitment of additional cortical areas. The main value of connectivity research in MS lies in its potential to capture sub- and premacroscopic pathology, which cannot be revealed by conventional MRI.

Abbreviations

CMCT	Central motor conduction time
CC	Corpus Callosum
DTI	Diffusion tensor imaging
EDSS	Expanded disability status scale
EEG	Electroencephalography
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging

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GM	Gray matter
ICC	Intracortical connectivity index
ICM	Interhemispheric coherence measure
IHI	Interhemisperic inhibition
iM1	Ipsilateral motor cortex
MD	Mean diffusivity
MEG	Magnetoencephalography
MEP	Motor evoked potential
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTR	Magnetization transfer ratio
NAWM	Normal appearing white matter
PASAT	Paced auditory serial addition task
PET	Positron emission tomography
QEEG	Quantitative EEG analysis
RRMS	Relapsing remitting multiple scleroseis
SI	Primary somatosensory cortex
SMC	Sensorimotor cortices
TMS	Transcranial magnetic stimulation
TBSS	Tract-based spatial statistics
WM	White matter

14.1 Introduction

In the developed world, multiple sclerosis (MS) is the most frequent neurological disease causing sustained disability in young adults. Previously, MS was considered an inflammatory demyelinating disease. However there is now evidence that axonal disconnection is already present in the earliest stages (Ferguson et al. 1997; Kuhlmann et al. 2002).

In the brains of patients with MS, changes in connectivity occur at all stages and types of the disease (Au Duong et al. 2005a; Audoin 2005; Helekar et al. 2010; Mainero et al. 2004). Research interest in the assessment of connectivity in the MS brain is rather intuitive as it is widely accepted that especially in the beginning of the disease inflammatory activity is high, a finding which has provoked a paradigm shift towards an early commencement of anti-inflammatory therapy. With increasing availability of anti-inflammatory agents yielding different levels of effectiveness but also different risk profiles, indices of early disease activity are needed to allow adjustment of treatment. In the field of neuroimaging, the vast majority of MS research has focused on white matter (WM) macrostructural pathology. Yet a great deal of early MS related changes might be found in the grey matter (GM) compartment of the brain and might be primarily functional in nature.

Connectivity in the MS brain can be assessed by modern neuroimaging techniques such as diffusion tensor imaging (DTI) and functional MRI (fMRI) as well as by neurophysiologic tools, namely Electroencephalography (EEG), Magnetoencephalography (MEG), and paired-coil transcranial magnetic stimulation (TMS). These techniques allow quantitative assessment of anatomic connectivity (strength of WM wiring), functional connectivity [temporal correlation of a neurophysiologic index measured in different brain areas (Friston et al. 1993)], and effective connectivity [influence that the activity of one neuronal system exerts directly or indirectly on the activity of another system (Friston et al. 1993)].

14.2 Conventional MRI-Disconnection Studies in MS

Until the establishment of structural and functional quantitative MRI techniques, connectivity research in MS was limited to study the behavioral consequences of T1 and T2 macroscopic lesions as detected by conventional MRI. To reveal clear behavioral/structural relations, lesions had to be located in strategic positions and cause well definable behavioral abnormalities, which were then characterized as "disconnection syndromes".

For example, a large WM lesion underlying the left supramarginal gyrus was detected by conventional MRI in one MS patient with clinical presentation of conduction aphasia (Arnett et al. 1996). Furthermore, a case of initial MS manifestation with right homonymous hemianopsia and alexia without agraphia, associated with concomitantly emerging lesions in the left occipital subcortical WM and the splenium of the corpus callosum (CC) was reported (Mao-Draayer and Panitch 2004). Also, conventional MRI revealed a lesion of the body of the CC in a left-handed male MS patient, who presented with peripheral agraphia, meaning that left-handed writing was neologistic, while oral spelling, typing, and spelling with the right hand were intact (Varley et al. 2005).

However, due to the high interindividual variability of lesion location, disconnection studies are typically limited to case reports and may reveal aspects of functional neuroanatomy rather than advancing knowledge of MS pathophysiology.

On a group analysis level, conventional MRI has been used to relate certain neurophysiologic and behavioral abnormalities to atrophy of defined WM structures such as the CC. As an indirect measure of interhemispheric disconnection, significant CC atrophy has been shown to be present even in mildly disabled patients (Barkhof et al. 1998; Pelletier et al. 1992; Rao et al. 1989). Atrophy of the splenium of the CC was associated with left ear extinction in the dichotic listening test and impaired name learning (Pelletier et al. 1992; Rao et al. 1989).

However, the promise of connectivity research in MS lies in its potential to capture sub- and premacroscopic pathology, which cannot be revealed by conventional MRI.

14.3 Anatomical Connectivity in MS

The study of anatomical connectivity in the brain using DTI has emerged as a useful tool also in MS research.

Based on diffusion weighted (DW) information, DTI measures molecule movement in several directions in space. In the human brain, molecular motion of free water is restricted by various physical barriers, e.g. cells, fibers and their microstructural components such as cell walls and membranous structures, resulting in higher molecular mobility alongside than perpendicular to the orientation of the main fiber bundle. DTI yields a map of directionality (anisotropy), which provides information about the microstructural organization and thus the connectivity of brain tissue (Le Bihan et al. 2001). The DTI measure most frequently used in the experimental setting is the fractional anisotropy (FA), which by measuring intra-voxel fiber coherence appears to be especially qualified to assess the strength of WM connections (Basser and Pierpaoli 1996; Pierpaoli et al. 1996) (Fig. 14.1).

DTI has been used to quantify connectivity changes within T1- and T2-visible lesions and also in the normal appearing white matter (NAWM) of patients with MS (Cercignani et al. 2001a, b; Droogan et al. 1999; Filippi et al. 2001; Horsfield et al. 1996; Iannucci et al. 2001; Werring et al. 2000). Consistently, the most severe diffusion changes have been found in T1-hypointense lesions (Droogan et al. 1999; Filippi et al. 2001; Werring et al. 1999). The heterogeneity of diffusion characteristics across different lesion subtypes might relate to different degrees of intralesional "dysconnectivity", with most severe chronic fiber degeneration within T1-hypointense lesions (van Walderveen et al. 1998).

Using whole brain FA-statistics, recent studies reported spatially widely distributed correlations of structural connectivity changes in patients with MS with clinical disability (Cader et al. 2007; Cercignani et al. 2001b). Dineen et al. (2009) employed tract-based spatial statistics (TBSS) to detect structural connectivity changes in WM tracts associated with cognitive dysfunction. The DTI-derived probabilistic WM connectome arising from regions of reduced FA was only partially related to areas of high FLAIR lesion probability, emphasizing the role of NAWM structural abnormalities in MS-related cognitive dysfunction. The close link between tract-specific DTI-derived measures and cognitive dysfunction shown in this study exemplarily indicates that DTI structural connectivity analysis might help to overcome the "MRI/Clinical paradox" which characterizes the repeated failure of conventional MRI to detect specific structural correlates of clinical disability in MS.

It is important to note that any result produced by whole brain DTI analysis will comprise areas of crossing fibers and complex fiber geometry and thus be highly contaminated by these non-biologic influences (Beaulieu 2002; Le Bihan 2003; Moseley et al. 1990). In other words, FA does not correlate linearly with the strength of WM wiring in areas where crossing fibers are present. For this reason interpretation of DTI connectivity data is less ambiguous when focusing on structures where fibers run parallel and crossing fibers are absent, such as the CC

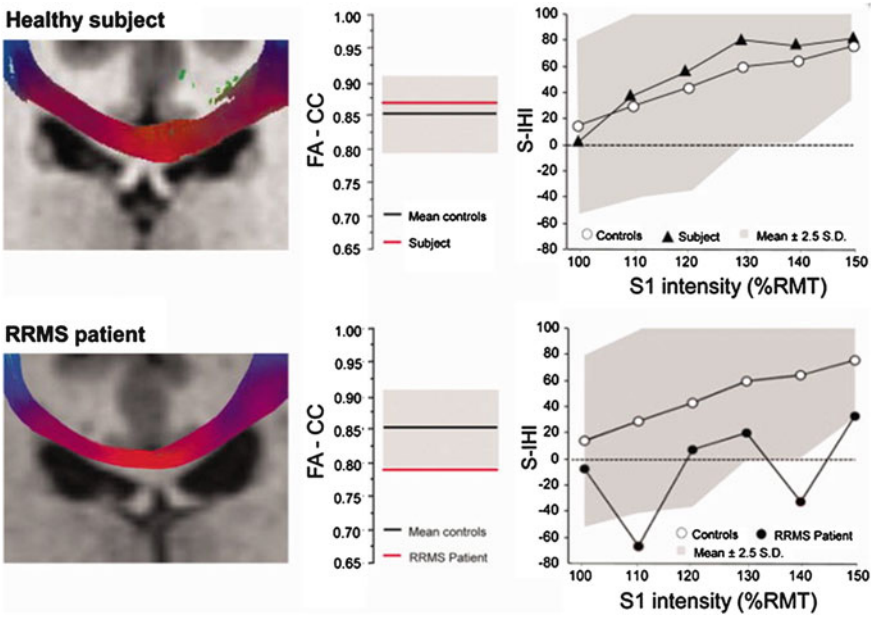

Fig. 14.1 This figure shows examples of the relation between macrostructural (MRI, DTI), microstructural (FA), and effective connectivity (Interhemispheric Inhibition = IHI) of callosal motor fibers (CMFs) of one healthy control (*upper row* of diagrams) and one RRMS patient (*lower row* of diagrams). Left panels: MRI shows individual hand CMFs as dissected in vivo by DTI fiber-tractography (coronal plane). *Middle panels*: the corresponding FA of the hand CMFs (*red lines*) are shown in relation to the mean ± 95 % CI (*black lines* and *gray areas*) of the healthy control group. *Right panels*: corresponding IHI (1 − conditioned MEP/unconditioned MEP) × 100 %, *y*-axis) is plotted against S1 intensity (in %RMT, *x*-axis) in relation to the mean IHI intensity curve (*white circles*), and 95 % CI (*gray area*) of the healthy control group. In the RRMS patient, normal CMF macroscopic appearance, but reduced FA and IHI was revealed

and the pyramidal tract. In the latter, FA and probabilistic tractography showed reduction in corticospinal connectivity in MS patients with a history of hemiparesis caused by lesions of the contralateral pyramidal tract (Gorgoraptis et al. 2010). Higher corticospinal tract connectivity inversely correlated with the degree of disability. An inverse correlation between FA and mean diffusivity (MD) in the cerebral peduncle with the pyramidal function score implemented as part of the expanded disability status scale (EDSS) to estimate motor impairment has also been demonstrated in MS patients (Ciccarelli et al. 2001).

In the CC, diffusion abnormalities are present early in the course of the disease, before any evidence of atrophy or macroscopic lesions (Ranjeva et al. 2003) or diffusion abnormalities in NAWM elsewhere in the brain (Ge et al. 2004). Yet, with regard to the possible interpretations of such findings, there is ambiguity as to whether these abnormalities reflect on site injury of the structure under investigation, or the secondary retrograde disconnection resulting from lesions in remote but connected brain areas and consecutive Wallerian axonal degeneration

(Ciccarelli et al. 2003). To address this question, DT-imaging can be used to perform tractographic dissection of specific fiber systems, as done for example for interhemispheric motor fibers (Wahl et al. 2011) in a group of patient with early RRMS. Patients with T1- and T2-visible lesions affecting this fiber system were excluded from FA analysis. A significant reduction of FA was revealed, providing evidence of "real NAWM degeneration", independent from directly co-localized or remotely related macroscopic pathology. The concept of tract-specific structural connectivity assessment is further supported by a study that revealed a significant correlation between abnormalities of the DTI apparent diffusion coefficient in the corticospinal tract and CC, with the pyramidal function system score and performance in the paced auditory serial addition task (PASAT). There was no correlation between corticospinal tract and CC T2 lesion load and the previously mentioned clinical scores, suggesting that DTI-based measures of microstructural connectivity are more strongly related to neurological dysfunction than conventional MRI parameters (Lin et al. 2005).

Using a voxel-based approach, (Ceccarelli et al. 2008) recently revealed regional differences in the distribution of MD changes in the NAWM patients with relapsing-remitting MS (RRMS) and benign MS (Ceccarelli et al. 2008). However, no between-group differences were detected when the average diffusivity was measured in the NAWM of the whole brain. These findings suggest that similar to T2-visible lesions, submacroscopic neurodegenerative pathology has certain foci rather than being globally and equally distributed in the brain.

In summary, DTI quantitative assessment offers a unique possibility to characterize patterns of submacroscopic dysconnectivity in MS as related to specific clinical deficits, especially when combined with DTI tractography.

14.4 Functional Cortical Activity, Functional Connectivity, and Effective Connectivity in MS

The vast majority of MS research has focused on WM structural changes whereas a great deal of early pathology might actually be occurring in the GM compartment and might have functional consequences. Especially, in the assessment of the correlates of cognitive impairment, which is highly prevalent in MS patients and significantly influences their everyday life (Chiaravalloti and DeLuca 2008; Patti 2009), conventional MRI seems to be insufficient. Originally used in basic Neurosciences to describe the spatio-temporal interactions of the neuronal activity in distributed neuronal networks, the term "Neuronal coordination" (Singer 1999; Uhlhaas and Singer 2006) has also emerged in MS-related research as a fundamental concept to describe higher cognitive functions (Ziemann et al. 2011). To assess and quantify basic measures of neuronal coordination, such as functional connectivity and effective connectivity, fMRI, EEG, MEG, and paired-coil TMS have been used.

14.4.1 FMRI Studies

Abnormalities of cognitive task-related fMRI activation and functional or effective connectivity have been shown in all stages and phenotypes of MS (Au Duong et al. 2005b; Audoin et al. 2005; Filippi and Rocca 2009; Helekar et al. 2010). The task-related abnormalities revealed in the MS brain are stronger activation of areas normally recruited by healthy individuals, increased connectivity, and recruitment of additional cortical areas (Au Duong et al. 2005b; Audoin et al. 2005; Giorgio et al. 2010; Rocca et al. 2005b, 2007; Staffen et al. 2002). Evidence for all three of these components was provided in a single cross-sectional fMRI study (Rocca et al. 2005a). Increased "orthotopic" activation of the primary sensorimotor cortex (SMC) and the supplementary motor area during performance of a given motor task was present at the earliest stage of the disease followed by bilateral activation patterns of these regions. At later stages widespread activation of additional areas, which in healthy people are usually recruited to perform novel/complex tasks, has been found (Rocca et al. 2005a).

From the behavioral perspective, enhanced cortical activation and recruitment of additional cortical areas might serve the purpose of limiting the behavioral manifestations of disease-related injury by supporting performance with a more widely distributed network. This view is supported by a longitudinal study, which revealed that increased levels of activation in the right lateral prefrontal cortices (LPFC) were associated with improved individual working memory and processing speed performance in patients with early MS after 12 months (Audoin et al. 2008).

In contrast, decreased task-related fMRI activity has been demonstrated in specific attention-related networks of MS patients with declining cognitive performance (Penner et al. 2003). In these patients, neither orthotopic overactivation nor recruitment of additional areas was found as opposed to mildly affected patients where increased and extended frontal and posterior parietal activation was revealed. These findings suggest that the capacity to integrate additional cortical nodes and to keep up a certain level of connectivity within this network might be exhausted during the course of the disease as cognitive decline becomes more evident. In line with these results, reduction of fMRI resting state activity in the anterior components of the default-mode network has been shown to be associated with cognitive deficits as assessed by the PASAT and word list test scores (Rocca et al. 2010).

While the available evidence supports the notion that neuronal overactivation, recruitment of additional cortical resources, and increased connectivity are effective compensatory mechanisms to maintain performance, whether or not these changes are associated with a beneficial outcome on the long run remains to be established. In fact there is evidence that short term recruitment of additional cortical resources may be beneficial if it is transient and followed by reallocation in the primary task-related areas. Following acute motor relapse secondary to pseudotumoral lesions, persistent recruitment of the primary SMC of the unaffected hemisphere was associated with poor clinical outcome, while re-

lateralization of movement-associated cortical activity in the primary SMC of the affected hemisphere predicted good clinical recovery (Mezzapesa et al. 2008).

The early and frequent involvement of the CC demonstrated by conventional MRI in MS provides the rational for extensive scrutiny of changes of interhemispheric functional interactions. Several recent fMRI studies revealed either reduced deactivation or increased activation of the ipsilateral M1 when an unimanual motor task was executed by MS patients (Lee et al. 2000; Manson et al. 2006, 2008; Mezzapesa et al. 2008; Pantano et al. 2002a, b; Reddy et al. 2000, 2002; Rocca et al. 2004; 2005b). However, due to the methodical limitations of fMRI, none of these studies prove that abnormal activation of the ipsilateral M1 is indeed attributable to dysfunctional interhemispheric motor inhibition rather than reflecting the consequence of adaptive reorganization of the cortical motor network, e.g., by unmasking ipsilateral corticospinal pathways. None of the studies mentioned above employed electrophysiological measures of interhemispheric effective connectivity.

14.4.2 Studies Employing Transcranial Magnetic Stimulation

One of the preferred sites to measure intercortical effective connectivity is the CC as it is known to be a focus of early disease activity. As a measure of transcallosal effective connectivity between M1, transcallosal inhibition has been measured in two different ways in MS patients. One way of testing transcallosal inhibition is the ipsilateral silent period (iSP) (Ferbert et al. 1992; Meyer and Roricht 1995; Meyer et al. 1998), which refers to a short attenuation or interruption of tonic voluntary EMG activity in a target muscle ipsilateral to the motor cortex stimulated by focal TMS. The duration and depth of iSP increases with the intensity of the magnetic stimulus. Several studies showed abnormally lengthened onset latency and/or prolonged duration of the iSP, suggestive of (Boroojerdi et al. 1998; Hoppner et al. 1999; Schmierer et al. 2000) but not specifically demonstrating a motor callosal conduction deficit in MS patients (Jung et al. 2006).

For example, Schmierer et al. (2000) demonstrated a higher frequency of iSP abnormalities compared to corticospinal conduction deficits. This indicates that functional cortico-cortical connectivity measures may be of superior sensitivity in detecting MS-related pathology compared to the established neurophysiologic markers such as central motor conduction time (CMCT) (Schmierer et al. 2000). Furthermore, a significant positive correlation between the degree of iSP prolongation and the burden of periventricular MRI detectable lesion load was revealed and transcallosal conduction deficits were therefore attributed to the heavy concentration of WM lesions in callosal and paraventricular locations. This study shows how MS-related abnormalities, not detectable by established neurophysiologic techniques, become accessible by the use of measures of cortico-cortical effective connectivity.

Another protocol probing interhemispheric motor connectivity in MS tests interhemisperic inhibition (IHI) by using paired pulse TMS. With this protocol, the inhibitory effect of a focal conditioning stimulus over the M1 hand area on the amplitude of the motor evoked potential (MEP) elicited by a test stimulus over the contralateral M1 hand area is tested (Ferbert et al. 1992). This protocol has recently been used to study two different phases of interhemispheric inhibition (short interval IHI and long interval IHI) in patients with early RRMS (Wahl et al. 2011). While IHI at short intervals was reduced in these patients, it was unaffected at long intervals, suggesting that besides the known differential structural vulnerability, certain functional systems may also be preferentially injured in the MS brain. Going beyond the investigation of interhemispheric M1–M1 connectivity, reduced functional excitatory connectivity between the dorsal premotor cortex (PMd) and the contralateral M1 was demonstrated in MS patients even in the absence of clinical disability (Codeca et al. 2010). With the manifestation of clinical disability in more advanced stages of the disease, the excitatory and inhibitory transcallosal connections originating from the PMd were compromised lending further credit to the perspective that there is a differential degree of vulnerability of distinct functional systems which can be affected at different time points in the course of the disease.

14.4.3 MEG and EEG Studies

Studies of brain connectivity based on hemodynamic principles (PET, fMRI) can be complemented by more direct measures of brain activity to complement their findings. Thus, the use of electrophysiological techniques has experienced an increase in the field of functional neuroimaging. Oscillatory electrical activity of the brain provides spatial and temporal information that might be crucial for the understanding of interaction and integration between neural networks (Basar et al. 1999).

MS is known as a "disconnection syndrome" and therefore, changes in different features of oscillatory neuronal activity provide evidence of impaired cortico-cortical and cortico-subcortical connectivity. There have been several studies investigating possible relationships between brain activity measured with EEG and MEG, and different MRI and clinical disease markers.

Quantitative EEG analysis (QEEG) has shown that RRMS patients display higher amplitudes in the beta and gamma frequency bands in the occipital bilateral and right frontal regions compared to benign MS patients and a group of healthy subjects (Vazquez-Marrufo et al. 2008). The observed changes in beta and gamma bands did not correlate with either disability scores or cognitive performance. The fact that RRMS and benign MS patients manifested different patterns of oscillatory brain activity suggests that reorganization processes may occur as a reaction to the more drastic brain injury in RRMS patients (Vazquez-Marrufo et al. 2008; Waxman 1997). These processes can be interpreted as an activation of compensatory mechanisms of the brain against impairment of cognitive functions

(Vazquez-Marrufo et al. 2008). Conversely, a high correlation between subcortical lesion load and reduction of EEG coherence was found in MS patients with cognitive impairemnt, suggesting that disconnection of cortical associative areas due to both axonal damage and demyelination in the subcortical WM might determine the degree of cognitive dysfunction (Leocani et al. 2000).

In RRMS patients, Cover et al. (2006) reported a decrease in the interhemispheric coherence measure (ICM) in the alpha band. Interestingly, ICM obtained using MEG was unrelated to clinical disability scores and to lesion load. Since neither alpha band power nor its distribution was significantly different between patients and the control group, it is plausible that the decrease in coherence indicates loss of connectivity as a consequence of demyelination and axonal degeneration (Cover et al. 2006). These results seem to support the idea that the neural architecture determines brain function, and hence that each particular neural process is the product of a distinct alliance between different cerebral cortical regions (Schmahmann and Pandya 2008). The functional connectivity of S1 and M1 has been assessed with MEG and using the *Morf_SM1* parameter that quantifies morphological distortions of topographical MEG maps (Dell'Acqua et al. 2010). It was found that even though S1 activation was not altered, the resulting somatosensory evoked field (SEF) was heavily distorted in RRMS patients. Moreover, the S1–M1 interaction was impaired, clearly indicating an intracortical network disruption. These changes were associated with a decreased volume of the left thalamus in the patient group, possibly related to wallerian degeneration of the corresponding fiber tracts (Houtchens et al. 2007).

In accordance with these findings, in a MEG study from the same group, a decreased intracortical connectivity index (ICC) in the primary somatosensory cortex (SI) was reported for RRMS patients. At the functional level, these changes were linked to a loss of functional specialization of the hand area as studied by electrical finger stimulation. Although a low positive correlation with lesion load was found, disease duration did not correlate with ICC alterations (Tecchio et al. 2008).

So far, the investigation of functional connectivity through EEG and MEG is proving to be a valuable tool in unraveling the mechanisms underlying the interaction of neural networks and information processing. Furthermore, assessment of brain activity with EEG and MEG is expected to yield new measures and indicators of the physiological alterations that are characteristic of the disease.

14.5 Combining Structural and Functional Connectivity Measures

Whether GM and WM abnormalities are parallel, or directly related processes—one causing the other—remains a matter of investigation. There are now a number of studies investigating the relationship between structural and functional connectivity in MS. Most of these studies are supportive of the view that changes of

functional or effective connectivity are secondary adaptive to structural disintegrity. These studies show that the task-related abnormalities detected in MS patients, namely overactivation of orthotopic areas, activation of additional areas, and increased connectivity (Au Duong et al. 2005a, b; Forn et al. 2007; Giorgio et al. 2010; Rocca et al. 2005a, 2007; Staffen et al. 2002) correlate with the extent of MRI measures of structural damage and disconnection (Au Duong et al. 2005a, b; Bobholz et al. 2006; Bonzano et al. 2009; Giorgio et al. 2010; Lowe et al. 2008; Rocca et al. 2007). Performing the PASAT, a widely used paradigm to assess working memory function, larger activations in bilateral Brodmann area 45 (BA45) were found in MS patients compared to controls. These activations inversely correlated with the mean NAWM magnetization transfer ratio (MTR) and the peak position of MTR in the GM. While the early multimodal studies correlated network-related fMRI activation in certain cortical nodes with global structural parameters, more recent approaches extracted DT-derived metrics from selected WM fiber bundles previously dissected by DTI tractography. In this way, network-specific correlations between functional and structural connectivity were revealed. For example, increased functional connectivity between the right primary SMC and the right cerebellum, and the left SMA and the left primary SMC inversely correlated with DTI indices of tissue damage of the corticospinal and the dentatorubrothalamic tract (Rocca et al. 2007). Again, changes of functional connectivity alongside with structural disconnection were demonstrated even in patients with normal behavioral performance, suggesting an adaptive role of functional connectivity changes to maintain normal cognitive or motor performance in the presence of structural damage. Clearly, in line with this assumption, another study showed increased task-related fMRI connectivity between several cortical areas of the sensorimotor network with the right inferior frontal gyrus and the right cerebellum, as well as decreased connectivity strengths with the anterior cingulate cortex in a group of patients with benign MS. A significant correlation of the coefficients of changed fMRI connectivity with structural MRI metrics of tissue damage was found within the tractographically dissected task-related WM network, but not with non-task-related WM fiber bundles. As correlations between functional and structural connectivity are not global, but specific for the network under investigation, the authors concluded that functional changes are specifically driven by damage within the related WM fiber bundle.

Since according to the definition of benign MS, patients had little or no clinical impairment even after a minimum disease duration of 15 years, this data may suggest that the severity of the disease course might be determined by the individual ability of limiting clinical manifestations by continued plastic adaptation of neuronal coordination within the GM compartment (Rocca et al. 2009).

While the studies mentioned above support the view that changes in GM functional connectivity follow WM disconnection, one recent study suggests a reciprocal if not converse causality. In this study, dissection of the WM working memory network using DTI tractography was performed to assess network-specific quantitative DWI metrics. While reduced FA and increased MD indicated structural disintegrity in the executive subsystem of the working memory, interthalamic structural

connectivity was increased in MS patients compared to control subjects suggesting presence of possible reactive WM structural plasticity (Audoin et al. 2007).

Due to the known pericallosal focus of disease activity in MS, the relation between functional and structural connectivity changes has also been studied in the interhemispheric motor network (Lenzi et al. 2007; Wahl et al. 2011). In a sample of relatively advanced RRMS patients, a multimodal approach comprising measures of fMRI activation, TMS effective connectivity, and DTI structural integrity was employed. In patients, increased MD and reduced FA were detected in the body of the CC along with a prolonged iSP duration and an increased (BOLD) activation in bilateral motor areas. A significant direct correlation between the MD of the CC and the amount of ipsilateral motor cortex (iM1) activation (fMRI) was found. There was an inverse correlation regarding the duration of iSP and the amount of iM1 activation (Lenzi et al. 2007). Functional changes in iM1 in patients with MS were interpreted as a consequence of the loss of transcallosal inhibitory connections. In line with these results, another recent study reported a significant correlation between FA of the transcallosal motor pathway and resting state functional connectivity of the bilateral primary sensorimotor cortices (SMC) as indicated by low-frequency BOLD fluctuations (LFBFs) in patients with MS (Lowe et al. 2008).

However, all of the studies mentioned hitherto showed correlations between GM functional connectivity changes and WM indices of structural disintegrity. Yet, one recent study performed dissection of the fiber system interconnecting M1 of the two hemispheres using DTI tractography and measured effective interhemispheric connectivity between M1 using paired pulse TMS (Wahl et al. 2011) Although this study showed reduction of both FA and IHI, it failed to show significant statistical relation between the microstructural connectivity marker FA and the functional connectivity marker IHI. This suggests that pathology in the MS brain cannot be entirely explained by the reciprocal reactive changes, but that processes in the GM and WM compartment are running parallel and independent from each other at least to some degree. Also, sensitivity analysis showed that IHI abnormalities were present in a higher percentage of patients compared to FA reduction, indicating that effective functional connectivity changes can be present before any detectable WM structural injury.

The combination of functional connectivity measures with indices of structural damage to specific WM fiber tracts is likely to advance our knowledge about the relationship between structural and functional abnormalities in MS.

References

Arnett PA, Rao SM, Hussain M, Swanson SJ, Hammeke TA (1996) Conduction aphasia in multiple sclerosis: a case report with MRI findings. Neurology 47:576–578

Au Duong MV, Audoin B, Boulanouar K, Ibarrola D, Malikova I, Confort-Gouny S, et al (2005a) Altered functional connectivity related to white matter changes inside the working memory network at the very early stage of MS. J Cereb Blood Flow Metab 25:1245–1253

Au Duong MV, Boulanouar K, Audoin B, Treseras S, Ibarrola D, Malikova I, et al (2005b) Modulation of effective connectivity inside the working memory network in patients at the earliest stage of multiple sclerosis. Neuroimage 24:533–538

Audoin B, Au Duong MV, Ranjeva JP, Ibarrola D, Malikova I, Confort-Gouny S, et al (2005) Magnetic resonance study of the influence of tissue damage and cortical reorganization on PASAT performance at the earliest stage of multiple sclerosis. Hum Brain Mapp 24:216–228

Audoin B, Guye M, Reuter F, Au Duong MV, Confort-Gouny S, Malikova I, et al. (2007) Structure of WM bundles constituting the working memory system in early multiple sclerosis: a quantitative DTI tractography study. Neuroimage 36:1324–1330

Audoin B, Reuter F, Duong MV, Malikova I, Confort-Gouny S, Cherif AA et al (2008) Efficiency of cognitive control recruitment in the very early stage of multiple sclerosis: a one-year fMRI follow-up study. Mult Scler 14:786–792

Barkhof FJ, Elton M, Lindeboom J, Tas MW, Schmidt WF, Hommes OR et al (1998) Functional correlates of callosal atrophy in relapsing-remitting multiple sclerosis patients. A preliminary MRI study. J Neurol 245:153–158

Basar E, Basar-Eroglu C, Karakas S, Schurmann M (1999) Are cognitive processes manifested in event-related gamma, alpha, theta and delta oscillations in the EEG? Neurosci Lett 259:165–168

Basser PJ, Pierpaoli C (1996) Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 111:209–219

Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system—a technical review. NMR Biomed 15:435–455

Bobholz JA, Rao SM, Lobeck L, Elsinger C, Gleason A, Kanz J et al (2006) fMRI study of episodic memory in relapsing-remitting MS: correlation with T2 lesion volume. Neurology 67:1640–1645

Bonzano L, Pardini M, Mancardi GL, Pizzorno M, Roccatagliata L (2009) Structural connectivity influences brain activation during PVSAT in multiple sclerosis. Neuroimage 44:9–15

Boroojerdi B, Hungs M, Mull M, Topper R, Noth J (1998) Interhemispheric inhibition in patients with multiple sclerosis. Electroencephalogr Clin Neurophysiol 109:230–237

Cader S, Johansen-Berg H, Wylezinska M, Palace J, Behrens TE, Smith S et al (2007) Discordant white matter *N*-acetylasparate and diffusion MRI measures suggest that chronic metabolic dysfunction contributes to axonal pathology in multiple sclerosis. Neuroimage 36:19–27

Ceccarelli A, Rocca MA, Pagani E, Ghezzi A, Capra R, Falini A et al (2008) The topographical distribution of tissue injury in benign MS: a 3T multiparametric MRI study. Neuroimage 39:1499–1509

Cercignani M, Bozzali M, Iannucci G, Comi G, Filippi M (2001a) Magnetisation transfer ratio and mean diffusivity of normal appearing white and grey matter from patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 70:311–317

Cercignani M, Inglese M, Pagani E, Comi G, Filippi M (2001b) Mean diffusivity and fractional anisotropy histograms of patients with multiple sclerosis. AJNR 22:952–958

Chiaravalloti ND, DeLuca J (2008) Cognitive impairment in multiple sclerosis. Lancet Neurol 7:1139–1151

Ciccarelli O, Werring DJ, Wheeler-Kingshott CA, Barker GJ, Parker GJ, Thompson AJ et al (2001) Investigation of MS normal-appearing brain using diffusion tensor MRI with clinical correlations. Neurology 56:926–933

Ciccarelli O, Werring DJ, Barker GJ, Griffin CM, Wheeler-Kingshott CA, Miller DH et al (2003) A study of the mechanisms of normal-appearing white matter damage in multiple sclerosis using diffusion tensor imaging—evidence of Wallerian degeneration. J Neurol 250:287–292

Codeca C, Mori F, Kusayanagi H, Monteleone F, Boffa L, Paolillo A et al (2010) Differential patterns of interhemispheric functional disconnection in mild and advanced multiple sclerosis. Mult Scler 16:1308–1316

Cover KS, Vrenken H, Geurts JJ, van Oosten BW, Jelles B, Polman CH et al (2006) Multiple sclerosis patients show a highly significant decrease in alpha band interhemispheric synchronization measured using MEG. Neuroimage 29:783–788

Dell'Acqua ML, Landi D, Zito G, Zappasodi F, Lupoi D, Rossini PM et al (2010) Thalamocortical sensorimotor circuit in multiple sclerosis: an integrated structural and electrophysiological assessment. Hum Brain Mapp 31:1588–1600

Dineen RA, Vilisaar J, Hlinka J, Bradshaw CM, Morgan PS, Constantinescu CS et al (2009) Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. Brain 132:239–249

Droogan AG, Clark CA, Werring DJ, Barker GJ, McDonald WI, Miller DH (1999) Comparison of multiple sclerosis clinical subgroups using navigated spin echo diffusion-weighted imaging. Magn Reson Imaging 17:653–661

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. J Physiol 453:525–546

Ferguson B, Matyszak MK, Esiri MM, Perry VH (1997) Axonal damage in acute multiple sclerosis lesions. Brain 120(Pt 3):393–399

Filippi M, Rocca MA (2009) Functional MR imaging in multiple sclerosis. Neuroimaging Clin N Am 19:59–70

Filippi M, Cercignani M, Inglese M, Horsfield MA, Comi G (2001) Diffusion tensor magnetic resonance imaging in multiple sclerosis. Neurology 56:304–311

Forn C, Barros-Loscertales A, Escudero J, Benlloch V, Campos S, Antonia Parcet M et al (2007) Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory N-back task. Hum Brain Mapp 28:424–430

Friston KJ, Frith CD, Liddle PF, Frackowiak RS (1993) Functional connectivity: the principal-component analysis of large (PET) data sets. J Cereb Blood Flow Metab 13:5–14

Ge Y, Law M, Johnson G, Herbert J, Babb JS, Mannon LJ et al (2004) Preferential occult injury of corpus callosum in multiple sclerosis measured by diffusion tensor imaging. J Magn Reson Imaging 20:1–7

Giorgio A, Portaccio E, Stromillo ML, Marino S, Zipoli V, Battaglini M et al (2010) Cortical functional reorganization and its relationship with brain structural damage in patients with benign multiple sclerosis. Mult Scler 16:1326–1334

Gorgoraptis N, Wheeler-Kingshott CA, Jenkins TM, Altmann DR, Miller DH, Thompson AJ et al (2010) Combining tractography and cortical measures to test system-specific hypotheses in multiple sclerosis. Mult Scler 16:555–565

Helekar SA, Shin JC, Mattson BJ, Bartley K, Stosic M, Saldana-King T et al (2010) Functional brain network changes associated with maintenance of cognitive function in multiple sclerosis. Front Hum Neurosci 4:219

Hoppner J, Kunesch E, Buchmann J, Hess A, Grossmann A, Benecke R (1999) Demyelination and axonal degeneration in corpus callosum assessed by analysis of transcallosally mediated inhibition in multiple sclerosis. Clin Neurophysiol 110:748–756

Horsfield MA, Lai M, Webb SL, Barker GJ, Tofts PS, Turner R et al (1996) Apparent diffusion coefficients in benign and secondary progressive multiple sclerosis by nuclear magnetic resonance. Magn Reson Med 36:393–400

Houtchens MK, Benedict RH, Killiany R, Sharma J, Jaisani Z, Singh B et al (2007) Thalamic atrophy and cognition in multiple sclerosis. Neurology 69:1213–1223

Iannucci G, Rovaris M, Giacomotti L, Comi G, Filippi M (2001) Correlation of multiple sclerosis measures derived from T2-weighted, T1-weighted, magnetization transfer, and diffusion tensor MR imaging. AJNR 22:1462–1467

Jung P, Beyerle A, Humpich M, Neumann-Haefelin T, Lanfermann H, Ziemann U (2006) Ipsilateral silent period: a marker of callosal conduction abnormality in early relapsing-remitting multiple sclerosis? J Neurol Sci 250:133–139

Kuhlmann T, Lingfeld G, Bitsch A, Schuchardt J, Bruck W (2002) Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. Brain 125:2202–2212

Le Bihan D (2003) Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci 4:469–480

Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N et al (2001) Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging 13:534–546

Lee M, Reddy H, Johansen-Berg H, Pendlebury S, Jenkinson M, Smith S et al (2000) The motor cortex shows adaptive functional changes to brain injury from multiple sclerosis. Ann Neurol 47:606–613

Lenzi D, Conte A, Mainero C, Frasca V, Fubelli F, Totaro P et al (2007) Effect of corpus callosum damage on ipsilateral motor activation in patients with multiple sclerosis: a functional and anatomical study. Hum Brain Mapp 28:636–644

Leocani L, Locatelli T, Martinelli V, Rovaris M, Falautano M, Filippi M et al (2000) Electroencephalographic coherence analysis in multiple sclerosis: correlation with clinical, neuropsychological, and MRI findings. J Neurol Neurosurg Psychiatry 69:192–198

Lin X, Tench CR, Morgan PS, Niepel G, Constantinescu CS (2005) 'Importance sampling' in MS: use of diffusion tensor tractography to quantify pathology related to specific impairment. J Neurol Sci 237:13–19

Lowe MJ, Beall EB, Sakaie KE, Koenig KA, Stone L, Marrie RA et al (2008) Resting state sensorimotor functional connectivity in multiple sclerosis inversely correlates with transcallosal motor pathway transverse diffusivity. Hum Brain Mapp 29:818–827

Mainero C, Caramia F, Pozzilli C, Pisani A, Pestalozza I, Borriello G et al (2004) fMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. Neuroimage 21:858–867

Manson SC, Palace J, Frank JA, Matthews PM (2006) Loss of interhemispheric inhibition in patients with multiple sclerosis is related to corpus callosum atrophy. Exp Brain Res 174:728–733

Manson SC, Wegner C, Filippi M, Barkhof F, Beckmann C, Ciccarelli O et al (2008) Impairment of movement-associated brain deactivation in multiple sclerosis: further evidence for a functional pathology of interhemispheric neuronal inhibition. Exp Brain Res 187:25–31

Mao-Draayer Y, Panitch H (2004) Alexia without agraphia in multiple sclerosis: case report with magnetic resonance imaging localization. Mult Scler 10:705–707

Meyer BU, Roricht S, von Grafin EH, Kruggel F, Weindl A (1995) Inhibitory and excitatory interhemispheric transfers between motor cortical areas in normal humans and patients with abnormalities of the corpus callosum. Brain 118(Pt 2):429–440

Meyer BU, Roricht S, Woiciechowsky C (1998) Topography of fibers in the human corpus callosum mediating interhemispheric inhibition between the motor cortices. Ann Neurol 43:360–369

Mezzapesa DM, Rocca MA, Rodegher M, Comi G, Filippi M (2008) Functional cortical changes of the sensorimotor network are associated with clinical recovery in multiple sclerosis. Hum Brain Mapp 29:562–573

Moseley ME, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari HS, Wendland MF et al (1990) Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology 176:439–445

Pantano P, Iannetti GD, Caramia F, Mainero C, Di Legge S, Bozzao L et al (2002a) Cortical motor reorganization after a single clinical attack of multiple sclerosis. Brain 125:1607–1615

Pantano P, Mainero C, Iannetti GD, Caramia F, Di Legge S, Piattella MC et al (2002b) Contribution of corticospinal tract damage to cortical motor reorganization after a single clinical attack of multiple sclerosis. Neuroimage 17:1837–1843

Patti F (2009) Cognitive impairment in multiple sclerosis. Mult Scler 15:2–8

Pelletier J, Habib M, Brouchon M, Poncet M, Lyon-Caen O, Salamon G et al (1992) Interhemispheric transfer in multiple sclerosis. Morphofunctional correlations. Rev Neurol 148:672–679

Penner IK, Rausch M, Kappos L, Opwis K, Radu EW (2003) Analysis of impairment related functional architecture in MS patients during performance of different attention tasks. J Neurol 250:461–472

Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996) Diffusion tensor MR imaging of the human brain. Radiology 201:637–648

Ranjeva JP, Pelletier J, Confort-Gouny S, Ibarrola D, Audoin B, Le Fur Y et al (2003) MRI/MRS of corpus callosum in patients with clinically isolated syndrome suggestive of multiple sclerosis. Mult Scler 9:554–565

Rao SM, Bernardin L, Leo GJ, Ellington L, Ryan SB, Burg LS (1989) Cerebral disconnection in multiple sclerosis. Relationship to atrophy of the corpus callosum. Arch Neurol 46:918–920

Reddy H, Narayanan S, Arnoutelis R, Jenkinson M, Antel J, Matthews PM et al (2000) Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis. Brain 123(Pt 11):2314–2320

Reddy H, Narayanan S, Woolrich M, Mitsumori T, Lapierre Y, Arnold DL et al (2002) Functional brain reorganization for hand movement in patients with multiple sclerosis: defining distinct effects of injury and disability. Brain 125:2646–2657

Rocca MA, Gallo A, Colombo B, Falini A, Scotti G, Comi G et al (2004) Pyramidal tract lesions and movement-associated cortical recruitment in patients with MS. Neuroimage 23:141–147

Rocca MA, Colombo B, Falini A, Ghezzi A, Martinelli V, Scotti G et al (2005a) Cortical adaptation in patients with MS: a cross-sectional functional MRI study of disease phenotypes. Lancet Neurol 4:618–626

Rocca MA, Mezzapesa DM, Ghezzi A, Falini A, Martinelli V, Scotti G et al (2005b) A widespread pattern of cortical activations in patients at presentation with clinically isolated symptoms is associated with evolution to definite multiple sclerosis. AJNR Am J Neuroradiol 26:1136–1139

Rocca MA, Pagani E, Absinta M, Valsasina P, Falini A, Scotti G et al (2007) Altered functional and structural connectivities in patients with MS: a 3-T study. Neurology 69:2136–2145

Rocca MA, Valsasina P, Ceccarelli A, Absinta M, Ghezzi A, Riccitelli G et al (2009) Structural and functional MRI correlates of Stroop control in benign MS. Hum Brain Mapp 30:276–290

Rocca MA, Absinta M, Moiola L, Ghezzi A, Colombo B, Martinelli V et al (2010) Functional and structural connectivity of the motor network in pediatric and adult-onset relapsing-remitting multiple sclerosis. Radiology 254:541–550

Schmahmann JD, Pandya DN (2008) Disconnection syndromes of basal ganglia, thalamus, and cerebrocerebellar systems. Cortex 44:1037–1066

Schmierer K, Niehaus L, Roricht S, Meyer BU (2000) Conduction deficits of callosal fibres in early multiple sclerosis. J Neurol Neurosurg Psychiatry 68:633–638

Singer W (1999) Neuronal synchrony: a versatile code for the definition of relations? Neuron 24(49–65):111–125

Staffen W, Mair A, Zauner H, Unterrainer J, Niederhofer H, Kutzelnigg A et al (2002) Cognitive function and fMRI in patients with multiple sclerosis: evidence for compensatory cortical activation during an attention task. Brain 125:1275–1282

Tecchio F, Zito G, Zappasodi F, Dell' Acqua ML, Landi D, Nardo D et al (2008) Intra-cortical connectivity in multiple sclerosis: a neurophysiological approach. Brain 131:1783–1792

Uhlhaas PJ, Singer W (2006) Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 52:155–168

van Walderveen MA, Kamphorst W, Scheltens P, van Waesberghe JH, Ravid R, Valk J et al (1998) Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. Neurology 50:1282–1288

Varley R, Cowell PE, Gibson A, Romanowski CA (2005) Disconnection agraphia in a case of multiple sclerosis: the isolation of letter movement plans from language. Neuropsychologia 43:1503–1513

Vazquez-Marrufo M, Gonzalez-Rosa JJ, Vaquero E, Duque P, Borges M, Gomez C et al (2008) Quantitative electroencephalography reveals different physiological profiles between benign and remitting-relapsing multiple sclerosis patients. BMC Neurol 8:44

Wahl M (2011) Motor callosal disconnection in early relapsing-remitting multiple sclerosis. Hum Brain Mapp 32:846–855

Waxman SG (1997) Molecular remodeling of neurons in multiple sclerosis: what we know, and what we must ask about brain plasticity in demyelinating diseases. Adv Neurol 73:109–120

Werring DJ, Clark CA, Barker GJ, Thompson AJ, Miller DH (1999) Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. Neurology 52:1626–1632

Werring DJ, Brassat D, Droogan AG, Clark CA, Symms MR, Barker GJ et al (2000) The pathogenesis of lesions and normal-appearing white matter changes in multiple sclerosis: a serial diffusion MRI study. Brain 123(Pt 8):1667–1676

Ziemann U, Wahl M, Hattingen E, Tumani H (2011) Development of biomarkers for multiple sclerosis as a neurodegenerative disorder. Prog Neurobiol 95:670–685

Chapter 15
Transcranial Magnetic Stimulation and Spinal Cord Injury

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Abstract During the last decades electrophysiological studies using transcranial magnetic stimulation (TMS) have demonstrated significant reorganization in the corticospinal system after human spinal cord injury (SCI). Evidence has shown that the latency and thresholds of motor evoked potentials (MEPs) elicited by TMS in upper and lower limb muscles are increased after SCI regardless of the time of injury. Electrophysiological studies indicated that corticospinal reorganization may contribute to aspects of functional recovery after SCI. Repetitive TMS has been used to induce long-lasting changes in corticospinal excitability and improvements in functional outcomes but their effect remains limited and inconsistent. Together, these studies revealed a large plastic capacity of the corticospinal system after SCI. Increasing our knowledge of the role of corticospinal plasticity in functional restoration after SCI may support the development of more effective therapeutic strategies.

15.1 Introduction

Spinal cord injury (SCI) affects around 12,000 individuals per year in the United States. These patients have limited motor function resulting in serious disability. During the past decades numerous experimental strategies—from neuroprotection to cell transplantation—have aimed at restoring SCI. However, these efforts have not resulted in an effective treatment for SCI. Currently rehabilitation strategies are

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the only available treatment. The success of rehabilitation strategies following SCI likely depends on the involvement of descending and spinal cord axonal pathways including the corticospinal system. Indeed, recent studies have demonstrated that aspects of corticospinal function can provide relevant information about the recovery of motor deficits after SCI.

TMS has been used most extensively for studying the corticospinal system, since the output of the primary motor cortex can be easily assessed in the form of motor evoked potential (MEP) by using electromyographic (EMG) recordings. This review will examine relevant studies that have used TMS in humans with SCI to examine aspects of motor cortical and corticospinal reorganization after injury. The possible role of transcranial magnetic stimulation (TMS) outcomes including MEPs latencies and thresholds as possible tools for clinical diagnosis and clinical research studies will be discussed. In addition, studies examining corticospinal function during different motor behaviors in patients with SCI will be reviewed. The overall aim of this chapter is to highlight the main aspects of motor cortical and corticospinal reorganization that are present at rest and during a motor task after human SCI.

15.2 Cortical and Corticospinal Reorganization After SCI

The corticospinal pathway undergoes reorganization after SCI (for review see Raineteau and Schwab 2001). Animal studies have shown that corticospinal neurons exhibit an extensive capacity for spontaneous sprouting (Fouad et al. 2001; Rosenzweig et al. 2010) and that axotomized axons can integrate into circuitries of intact spinal cord segments (Ghosh et al. 2010). Indeed, it has been demonstrated that injured corticospinal neurons are able to sprout rostral (Fouad et al. 2001) and caudal (Weidner et al. 2001) to a spinal cord lesion. Even some corticospinal tract collaterals rostral to the lesion can connect onto spared propriospinal interneurons and form new intraspinal circuits (Bareyre et al. 2004) that might be functionally meaningful (Vavrek et al. 2006). Sprouting and anatomical reorganization has also been shown to occur in unlesioned descending tracts such as the rubrospinal tract after transection of the corticospinal tract which is referred to as a collateral sprouting (Raineteau et al. 2002).

TMS has emerged as an important non-invasive tool to investigate the contribution of the corticospinal tract to human motor control. Evidence has shown that TMS can access direct corticomotoneuronal cells as well as disynaptic pathways that may contribute to the size of MEPs (for reviews see Petersen et al. 2003, 2010). It was not until the late twentieth century that the first studies using TMS in humans with SCI were published (Levy et al. 1990; Topka et al. 1991; Brouwer et al. 1992), providing evidence that this method can be a useful tool to contribute to understanding mechanisms involved in cortical and corticospinal reorganization after SCI. Levy and collaborators (Ghosh et al. 1990, 2010) demonstrated in two quadriplegic patients who regained some voluntary control in proximal arm

muscles while the distal muscles remained paretic that MEPs could be elicited in proximal muscles from a much wider area of the scalp than in control subjects. Similarly, Topka et al. (1991) showed that MEPs recorded from muscles in the abdominal wall rostral to the injury site were elicited from a larger number of scalp positions compared to controls. Brouwer et al. (1992) demonstrated that the short latency facilitation of MEPs in lower limb muscles, reflecting activation of the fast corticospinal pathway, was present in patients with acute and chronic injuries at delayed latencies. Since 1992, a large number of studies have proposed that TMS outcomes, including MEPs latencies and thresholds, can be used as possible tools for clinical diagnosis and clinical research studies (for reviews see Kirshblum et al. 1998; Ellaway et al. 2004, 2007). In addition, TMS has also been used to decrease spasticity and improve motor function after SCI (Belci et al. 2004; Kumru et al. 2010).

MEP latencies after SCI. One of the important pathological processes affecting the white matter after SCI is a chronic and progressive demyelination of long motor axons (Griffiths and McCulloch 1983; Bunge et al. 1993; Totoiu and Keirstead 2005). Histological examination in animal and human tissue has shown that after SCI myelin loss is more pronounced in large diameter fibers (Blight and Young 1989; Quencer et al. 1992). In humans, transmission in large diameter fast conducting fibers can be assessed by using TMS (Brouwer et al. 1992). Therefore, changes in MEP onset latency can provide an estimate of the impairment of the fastest conducting corticospinal neurons. It is important to consider that the latency of EMG responses to TMS applied over the primary motor cortex depends on several factors including the stimulus intensity, size of response, voluntary pre-activation of the muscle and intactness of the corticospinal system. The MEP latency on voluntary active muscles are shorter (as much as 4 ms) than those recorded in relaxed muscles for a given stimulus intensity (for review see Rothwell et al. 1999), which may be in part related to the size principle of motor unit recruitment, the existence of a synaptic relay, and the presence of multiple descending volleys.

The majority of studies using TMS in patients with incomplete SCI have reported delayed MEP latencies in partially paralyzed muscles regardless of the time after injury. For example, Curt et al. (1998) demonstrated in a mixed group of cervical and thoracic SCI patients that MEP latencies were delayed by around 10 ms compared to controls and these values did not change from the initial assessment on the day of injury in a 6-month follow-up period. Studies in which the SCI post-injury time ranged from 19 days to just over a year have reported that the onset latency of distal arm and leg muscles is delayed by around 10 ms (Alexeeva et al. 1998; Davey et al. 1998; Smith et al. 2000). Alexeeva et al. (1998) conducted a comprehensive study looking at MEP onset latencies after cervical SCI in individuals ranging from 1 day to 6.5 years post-injury in several upper and lower limb muscles. The authors reported that in the acute and chronic phase of SCI the MEP latency was delayed by approximately 2–15 ms in all muscles tested. Comparisons of MEPs latencies taken at different time points after injury in the

same patients did not reveal consistent differences despite the fact that patients improved their EMG recruitment patterns.

Investigations including muscles other than that of the upper and lower limb, but with the same post-injury time, have also revealed delay times in MEP latency in patients with SCI. Lissens and Vanderstraten (1996) examined MEP latency in primary inspiratory and expiratory muscles (diaphragm, scalene, and parasternal) in 4 cervical SCI patients. During inspiration and expiration, MEPs were delayed by approximately 2–3 ms in patients compared to the control group. However, no latency delays were found in the diaphragm at either stage of respiration. Cariga et al. (2002) recorded MEPs from paravertebral muscles at 12 thoracic levels of thoracic SCI patients (time post-injury: 0.3–19.9 years). The authors found onset latency delays of around 7–8 ms below the level of the injury and also in muscle representations located above the injury level. It was suggested that the severe axonal damage caused a reduction in conduction velocity of the surviving central component. Recent studies continue to report similar delayed latencies of 7–8 ms in lower limb (Barthelemy et al. 2010) and upper limb muscles (Roy et al. 2011) in a mix of thoracic, cervical, and lumbar SCI patients, with a post-injury average time of >1 year.

Methodological aspects make it difficult to compare latencies across injury time since several studies combined the results from individuals with acute and chronic SCI and used different stimulus intensities to perform the testing. However, the published evidence together suggests that after SCI delays in MEP latency can vary from 2 to 10 ms depending on the muscle representation tested.

MEP threshold after SCI. According to the international federation of clinical neurophysiology guidelines (Rothwell et al. 1999), resting motor threshold is defined as the minimum stimulus intensity required to elicit MEPs greater than 50 μV peak-to-peak amplitude in at least 5 out of 10 consecutive trials in the relaxed muscle. During this measurement the initial cortical elements activated by TMS are likely to be large diameter myelinated axons but it is important to consider that MEPs are evoked after a sequence of synaptic relays that can occur at the level of cortex and spinal cord. Therefore, even though the threshold of the cortical axons is likely to depend on the level of synaptic activity in the cortex, the MEP threshold will also depend on the excitability of synaptic relays. Threshold is probably best measured during active muscle contraction, when synaptic activity is better defined. The active motor threshold is defined as the minimal stimulus intensity able to evoke MEPs bigger than 100–200 μV peak-to-peak amplitude in at least 5 out of 10 consecutive trials during ∼10 % of MVC. During voluntary activity, the motor threshold is affected by administration of CNS acting as drugs that affect membrane excitability, whereas drugs that affect synaptic transmission have little influence (Ziemann et al. 1996a, b).

Most studies using TMS have reported that resting and active motor thresholds are increased in individuals with incomplete SCI regardless of the time since the injury, possibly as a result of reduced numbers of corticospinal axons reaching the pool of motoneurons. Smith et al. (2000) completed a longitudinal study in 21 patients with incomplete SCI and demonstrated that the motor thresholds tested at

rest or during a small voluntary contraction were significantly increased in patients with injury times varying from around 1 to 300 days. Similarly, in patients with cervical SCI with a post-injury time from 90 to 852 days, resting and active motor thresholds were increased compared to controls in finger muscles (Davey et al. 1998, 1999). It is important to consider that the motor threshold may be also related to the degree of impairment; patients with small motor impairment can show thresholds that are similar to controls (Bunday and Perez 2012).

Motor cortical inhibition after SCI. In humans, GABAergic intracortical inhibition can be examined using a paired-pulse TMS protocol (Kujirai et al. 1993). A subthreshold, conditioning TMS pulse decreases the size of an MEP elicited by a later suprathreshold test stimulus when applied over the primary motor cortex. This effect can be observed at conditioning time intervals between 1 and 5 ms. The intensity of the conditioning stimulus was below the threshold for activating motoneurons, therefore, it was suggested that this effect was occurring at the cortical level. Later evidence (Di Lazzaro et al. 1998) confirmed the cortical origin of short-interval intracortical inhibition (SICI) demonstrating that a subthreshold conditioning stimulus which itself did not evoke motoneuronal activation produced a clear suppression of late I-waves if the interval between the stimuli was between 1 and 5 ms. Subsequent studies have shown that administration of a single oral dose of a GABAa agonists increases the amount of SICI and also increases the inhibition of later descending I-waves (for review see Reis et al. 2008).

Only a few studies have used the paired-pulse TMS protocol to examine SICI in patients with SCI. The findings demonstrated that although the magnitude of SICI is reduced in patients with incomplete SCI compared to control subjects (Shimizu et al. 2000; Saturno et al. 2008; Roy et al. 2011), the relative excitability profile of cortical inhibitory circuits is unchanged (Roy et al. 2011). Some important considerations need to be taken into account when examining these studies. First, Shimizu et al. (2000) and Saturno et al. (2008) only tested SICI in one single patient with SCI and observed different results. Shimizu et al. (2000) showed the presence of SICI, but to a lesser extent than controls, only at 3 ms conditioning test interval using an intensity of 80 % of resting motor threshold for the conditioning pulse. Saturno et al. (2008) reported no inhibition in the patient with SCI compared to controls at any conditioning test interval tested by using an intensity of 95 % of resting motor threshold for the conditioning pulse. Second, since in both studies control experiments were not conducted for the intensities used for the test and conditioning pulse, it cannot be excluded that the parameters used for testing recruited a mixture of inhibition, facilitation, or were not effective (Ortu et al. 2008). Roy et al. (2011) controlled for testing parameters during the examination of SICI in patients with SCI. While only four patients were tested (testing was done bilaterally), SICI was present at a conditioning test interval of 3 ms in a hand muscle. Importantly, here no control data was reported in the same muscle representation for comparison. However, in a leg muscle, SICI was less pronounced than in a hand muscle and it was also decreased in SCI patients compared to controls.

Stimulus intensities below threshold can reduce the ongoing EMG activity during a voluntary contraction (Davey et al. 1994). It is thought that suppression of ongoing corticospinal excitation to motoneurons occurs by activation of intracortical inhibitory circuits. Recent data demonstrated that low-intensity cortical stimulation inhibits ongoing EMG activity in fast-conducting corticospinal axons through an oligosynaptic pathway (possibly disynaptic), and that this activity contributes to drive the motoneurons during voluntary contractions (Butler et al. 2007). In patients with SCI, the latency of such inhibition was increased compared to controls (Davey et al. 1998; Smith et al. 2000), suggesting that the early portion of the inhibitory process became weaker or absent after injury. Specifically, in patients with SCI, the onset of EMG suppression is around 25 ms longer than the latency of the MEP, while the latency difference is only around 13 ms in controls (Davey et al. 1998; Smith et al. 2000). An alternative possibility is that a greater involvement of slow conducting corticospinal axons during voluntary activity after SCI may also contribute to the increased latency in the EMG suppression elicited by subthreshold TMS. Therefore, even though all these studies together suggests that after SCI there is an impaired modulation of intracortical inhibitory pathways, it is also clear that more evidence needs to be accumulated to ensure the extent to which SICI is affected by an injury to the spinal cord.

15.3 Motor Actions and Corticospinal Reorganization After SCI

A few studies have examined cortical and corticospinal reorganization in patients with SCI during a motor task. Corticospinal reorganization associated with recovery of motor function may be reflected by changes in recruitment order of motoneurons. Davey et al. (1999) tested the effect of increasing levels of isometric voluntary contraction with thenar muscles on the size of MEPs elicited in the same contracting muscle. All patients tested had a SCI rostral to C8-T1 segments, which supply the thenar muscles. It was found that patients showed a less pronounced increase in MEP size with increasing TMS stimulus intensity and also with increasing amount of voluntary contraction compared to controls. Specifically, at stimulus intensities of 120 % resting motor threshold and above, patients with SCI showed significantly smaller MEPs relative to the maximum ulnar nerve M-wave response than controls. In addition, patients showed a less steep pattern of increments in MEP size with increasing levels of voluntary contraction compared to controls. While in patients MEP size continued to increase up to 50 % of maximum voluntary contraction, MEP size reached a plateau around 10 % of maximum voluntary contraction in control subjects (see Fig. 15.1). It is possible that, after SCI, for a muscle to function over its entire effective range, changes in reorganization of connections within the corticospinal system are needed. This might be accomplished by inputs from other descending or segmental inputs that

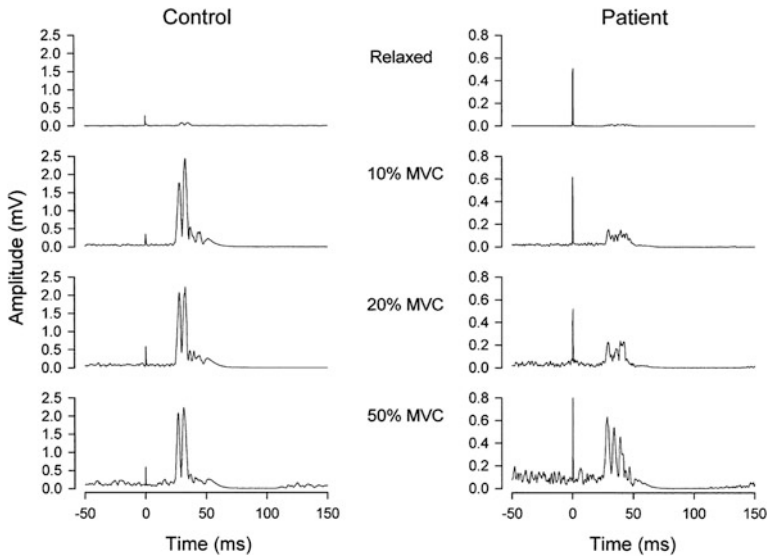

Fig. 15.1 Average rectified responses of thenar muscles to TMS, evoked at four different stimulus intensities, in a control subject and a patient with SCI while maintaining a voluntary contraction of 15 % of maximal voluntary contraction (MVC). The active motor threshold (T) for a MEP response at 15 % of MVC was 30 % of the maximal stimulator output in the control and 40 % of the maximal stimulator output in the patient. Each record is an average of between 10 and 20 responses. Note the smaller *y*-axis scaling in the patient. Also note that the increase in the MEP size with increasing stimulus strengths is less marked in the patient compared to the control subject. (Modified from Davey et al. 1999)

contribute to increase the drive to spinal motoneurons while the remaining corticospinal output contributes to modulate the voluntary contraction.

Another study used TMS during locomotion in patients with chronic incomplete SCI. It was reported that parameters such as MEP amplitude at rest and MEP latency during a voluntary contraction correlated with the degree of foot drop in patients with SCI (Barthélemy et al. 2010). This suggests that transmission in corticospinal drive to lower limb spinal motoneurons of the muscles tested is of functional importance for lifting the foot during the early swing phase of the gait cycle. Importantly, these results demonstrated a linkage between electrophysiological measurements of corticospinal function examined by TMS and a behavioral deficit observed during locomotion in patients with SCI. This is also in agreement with a previous study (Thomas and Gorassini 2005) demonstrating that 3–5 months of locomotor training can enhance measurements of corticospinal function, such as the size of the maximal MEP tested by TMS and the slope of input–output excitability recruitment curves of lower limb muscles in patients with incomplete SCI. Although a correlation does not prove causality, an important finding in this study was that the percentage changes observed in MEP size in lower limb muscles was correlated to the improvements in locomotor ability

observed in these patients. This suggests that the recovery of locomotion was, at least in part, mediated by changes in corticospinal function.

A more recent study tested MEPs in a resting hand muscle during increasing levels of isometric voluntary contraction by a contralateral finger muscle and a more proximal arm muscle (Bunday and Perez 2012). In this study 14 patients with chronic cervical incomplete SCI were tested and it was shown that the size of MEPs measured in the resting hand remained unchanged during increasing levels of voluntary contraction with a contralateral distal or proximal arm muscle. In contrast, MEP size in a resting hand muscle was increased during the same motor tasks in controls. Figure 15.2 shows the raw and group data in patients with cervical SCI and in control subjects demonstrating that MEP size was increased in a resting hand muscle during contralateral 70 % of maximum voluntary contraction exerted by either a finger muscle or the biceps brachii in controls but not in patients with cervical SCI. To examine the mechanisms contributing to the increase in MEP size, in the same study the authors examined SICI and motoneuronal behavior by testing F-waves and cervicomedullary MEPs (CMEPs). SICI during contraction of the contralateral arm muscles were unchanged after cervical SCI and decreased in healthy controls (Fig. 15.3). F-waves amplitude and persistence, and CMEPs size remained unchanged after cervical SCI and increased in healthy controls. It is suggested that impairments in GABAergic intracortical inhibition and excitability of index finger motoneurons are neural mechanisms underlying, at least in part, the lack of crossed corticospinal facilitation observed after chronic cervical SCI. Overall, the results from these studies have increased our understanding of how the reorganized corticospinal pathway responds to voluntary activity during a motor task. However, it is also clear that a better understanding of involvement of the reorganized corticospinal pathways in functionally relevant tasks is especially important for elucidating its role in recovery after human SCI.

15.4 Effects of Repetitive Non-Invasive Brain Stimulation After SCI

Repetitive TMS (rTMS) after SCI. A large number of studies have examined the effects of rTMS on the excitability of the hand and leg motor representations in the primary motor cortex in control subjects. The nature of the after-effects of rTMS depends on the number, intensity, and frequency of stimulation. Stimulation of the primary motor cortex at a subthreshold intensity and at a frequency of 1 Hz for about 25 min (1,500 total stimuli) in general reduced the size of MEPs evoked in finger muscles for the next 30 min (Chen et al. 1997), while stimulation at frequencies higher than 1 Hz tend to increase corticospinal excitability. The after-effects of rTMS also depend on the pattern of the individual TMS pulses. Huang et al. (2005) used theta-burst stimulation (TBS), a protocol in which three 50 Hz

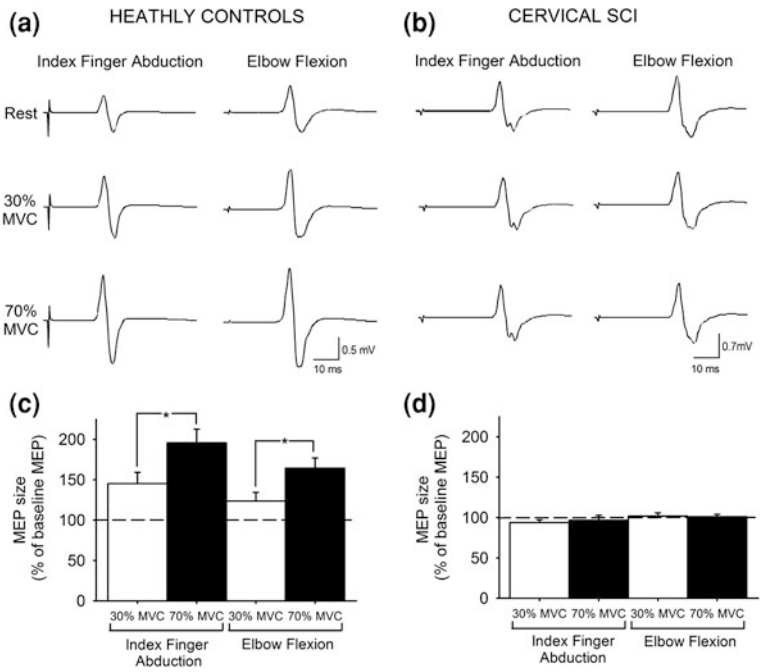

Fig. 15.2 Motor evoked potentials (MEPs). Subjects were instructed to keep one hand at rest while the other side remained at rest or performed 30 and 70 % of their maximal voluntary contraction (MVC) for index finger abduction or elbow flexion by activating the first dorsal interosseous (FDI) and biceps brachii muscles, respectively. The condition in which both arms remained at rest was used as a baseline. MEPs recorded from the resting first dorsal interosseous (FDI) of a representative healthy control (**a**) and in a patient with cervical SCI (**b**) while the other side remained at rest or performed 30 or 70 % of index finger abduction or elbow flexion. Group data (**c**, Healthy controls, $n = 10$; **d**, Cervical SCI, $n = 14$). The abscissa shows the MVC levels tested (30 % of MVC, *black bars*; 70 % of MVC, *white bars*). The ordinate shows the size of the FDI MEP as a percentage of the baseline FDI MEP. Note the increase in FDI MEP size during contralateral index finger abduction and elbow flexion in healthy controls and after thoracic but not cervical SCI. Error *bars* indicate SEs. $^*P < 0.05$. (Modified from Bunday and Perez 2012)

pulses are applied regularly five times per second for 20–40 s. In this protocol, low intensities of stimulation produces suppression of motor cortex excitability as measured by MEP size. However, if each TBS burst is applied for only 2 s followed by a pause of 8 s and is repeated, after the effect becomes facilitatory.

While previous studies have been successful in demonstrating that rTMS applied over the motor cortex results in significant improvements in aspects of hand motor function in patients with motor disorders including stroke, Parkinson's disease, multiple sclerosis, and dystonia, the effects of rTMS after SCI are less explored and more controversial. Belci et al. (2004) demonstrated for the first time in subjects with chronic (>1 year) incomplete SCI that application of rTMS over the motor cortex altered cortical inhibition and improved clinical and functional outcomes, suggesting the potential beneficial effect of this technique in this patient

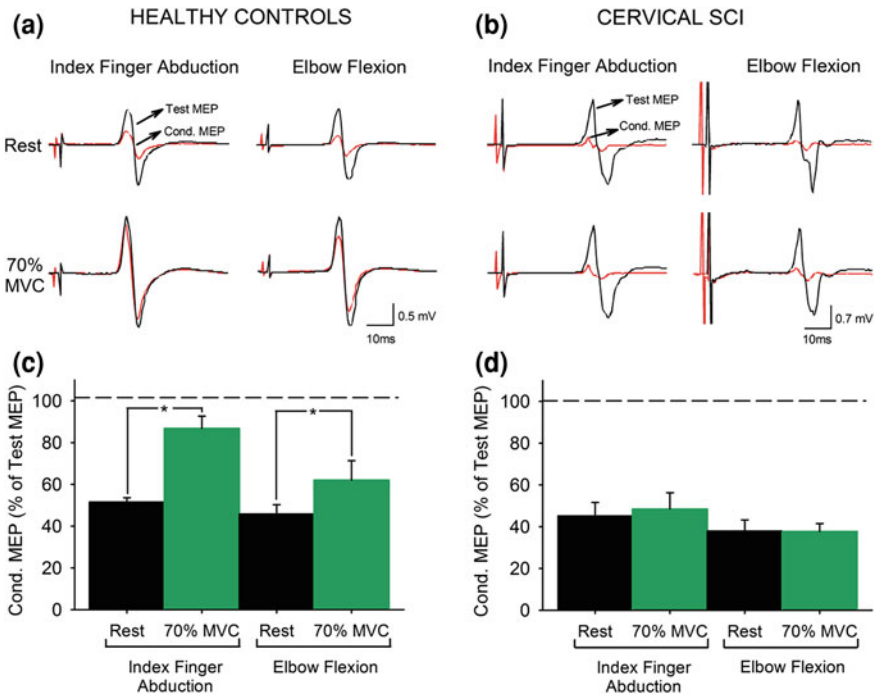

Fig. 15.3 Short-interval intracortical inhibition (SICI). SICI recorded from the resting FDI of representative healthy control (**a**) and in a patient with cervical SCI (**b**). The test MEP (*black traces*) and conditioned MEP (Cond. MEP, *red traces*) are indicated by *black arrows*. Group data (**c**, Healthy controls, $n = 8$; **d**, Cervical SCI, $n = 8$). The abscissa shows all conditions tested (rest, *black bars*; 70 % of MVC, *green bars*). The ordinate shows the magnitude of the conditioned MEP expressed as a percentage of the test MEP. The horizontal *dashed line* represents the size of the Test MEP. Note that SICI decreased during index finger abduction and elbow flexion of the contralateral arm in healthy controls but not after cervical SCI. Error *bars* indicate SEs. $*P < 0.05$. (Modified from Bunday and Perez 2012)

population. In this study four stable patients with incomplete SCI were tested and received 5 days of sham rTMS delivered over the occipital cortex followed by 5 days of therapeutic stimulation delivered over the primary motor cortex. rTMS consisted of double TMS pulses applied separated by 100 ms (10 Hz) at a frequency of 0.1 Hz (10 s interval), over five consecutive days with each session lasting for 1 h (a total of 360 doublet pulses) at an intensity of 90 % of the resting motor threshold. After rTMS, the contralateral silent period, a measurement that in part reflects cortical changes, was decreased compared to pre-intervention values and returned to baseline after a follow up of 3 weeks. It was reported that these cortical changes were associated with improvement in clinical measures of motor and sensory function.

More recently, Kuppuswamy et al. (2011) tested the effect of 5 Hz rTMS in 23 adults with chronic (>9 months), stable complete or incomplete SCI, and a lesion

level of T1 or above with residual hand and arm motor function. rTMS was delivered at 5 Hz and 2 s trains were separated by 8 s for 15 min, at an intensity of 80 % of the active motor threshold over five consecutive days. Sham stimulation was provided using a circular sham coil placed over the vertex. These authors reported that the stimulation parameters used in this study produced no changes in the clinical neurological assessment of patients with SCI. There were only modest functional gains that were not significantly different from sham treatment. The active motor threshold was the only test conducted using single pulse TMS that showed differences after the rTMS protocol.

rTMS has also been used with the goal of decreasing spasticity in patients with motor disorders. Indeed, previous studies have shown that high-frequency rTMS applied over the motor cortex can decrease the size of the H-reflex in control subjects (Valero-Cabre et al. 2001; Perez et al. 2005) and decreases spasticity in patients (Centonze et al. 2007; Valle et al. 2007). Centonze et al. (2007) observed an improvement in lower limb spasticity after 2 weeks of daily rTMS sessions consisting of 5 Hz stimulation at intensity of 100 % of the resting motor threshold over the leg representation of the primary motor cortex in patients with multiple sclerosis. In agreement, in the same patient population, rTMS applied over the thoracic spine showed also some effects in decreasing spasticity (Nielsen et al. 1996). Valle et al. (2007) showed in children with spastic quadriplegia a clinically significant effect of rTMS in decreasing spasticity. More recently, it was demonstrated that after 1 week of daily sessions of 20 Hz rTMS stimulation at 90 % of resting motor threshold over the leg representation of the primary motor cortex, spasticity was decreased and the effect was maintained for at least 1 week after stimulation in patients with incomplete SCI (Kumru et al. 2010).

Although most of these data point toward a beneficial effect of rTMS on spasticity further systematic studies are needed to examine more in-depth mechanistic insights underlying the effects of rTMS in humans with incomplete SCI to explore their possible clinical benefits for patients with spasticity.

References

Alexeeva N, Broton JG, Calancie B (1998) Latency of changes in spinal motoneuron excitability evoked by transcranial magnetic brain stimulation in spinal cord injured individuals. Electroencephalogr Clin Neurophysiol 109:297–303

Bareyre FM, Kerschensteiner M, Raineteau O, Mettenleiter TC, Weinmann O, Schwab ME (2004) The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats. Nat Neurosci 7:269–277

Barthélemy D, Willerslev-Olsen M, Lundell H, Conway BA, Knudsen H, Biering-Sørensen F, Nielsen JB (2010) Impaired transmission in the corticospinal tract and gait disability in spinal cord injured persons. J Neurophysiol 104:1167–1176

Belci M, Catley M, Husain M, Frankel HL, Davey NJ (2004) Magnetic brain stimulation can improve clinical outcome in incomplete spinal cord injured patients. Spinal Cord 42:417–419

Blight AR, Young W (1989) Central axons in injured cat spinal cord recover electrophysiological function following remyelination by Schwann cells. J Neurol Sci 91:15–34

Brouwer B, Bugaresti J, Ashby P (1992) Changes in corticospinal facilitation of lower limb spinal motor neurons after spinal cord lesions. J Neurol Neurosurg Psychiatry 55:20–24

Bunday KL, Perez MA (2012) Impaired crossed facilitation of the corticospinal pathway after cervical spinal cord injury. J Neurophysiol (in press)

Bunge RP, Puckett WR, Becerra JL, Marcello A, Quencer RM (1993) Observation on the pathology of human spinal cord injury. A review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelinization. In: Seil FJ (ed) Advances in Neurology. Raven Press, New York, pp 75–89

Butler JE, Larsen TS, Gandevia SC, Petersen NT (2007) The nature of corticospinal paths driving human motoneurones during voluntary contractions. J Physiol 584:651–659

Cariga P, Catley M, Nowicky AV, Savic G, Ellaway PH, Davey NJ (2002) Segmental recording of cortical motor evoked potentials from thoracic paravertebral myotomes in complete spinal cord injury. Spine (Phila Pa 1976) 27:1438–1443

Centonze D, Koch G, Versace V et al (2007) Repetitive transcranial magnetic stimulation of the motor cortex ameliorates spasticity in multiple sclerosis. Neurology 68:1045–1050

Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 48:1398–1403

Curt A, Keck ME, Dietz V (1998) Functional outcome following spinal cord injury: significance of motor-evoked potentials and ASIA scores. Arch Phys Med Rehabil 79:81–86

Davey NJ, Romaiguere P, Maskill DW, Ellaway PH (1994) Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. J Physiol 477:223–235

Davey NJ, Smith HC, Wells E, Maskill DW, Savic G, Ellaway PH, Frankel HL (1998) Responses of thenar muscles to transcranial magnetic stimulation of the motor cortex in patients with incomplete spinal cord injury. J Neurol Neurosurg Psychiatry 65:80–87

Davey NJ, Smith HC, Savic G, Maskill DW, Ellaway PH, Frankel HL (1999) Comparison of input–output patterns in the corticospinal system of normal subjects and incomplete spinal cord injured patients. Exp Brain Res 127:382–390

Di Lazzaro V, Restuccia D, Oliviero A, Profice P, Ferrara L, Insola A, Mazzone P, Tonali P, Rothwell JC (1998) Magnetic transcranial stimulation at intensities below active motor threshold activates intracortical inhibitory circuits. Exp Brain Res 119:265–268

Ellaway PH, Anand P, Bergstrom EM, Catley M, Davey NJ, Frankel HL, Jamous A, Mathias C, Nicotra A, Savic G, Short D, Theodorou S (2004) Towards improved clinical and physiological assessments of recovery in spinal cord injury: a clinical initiative. Spinal Cord 42:325–337

Ellaway PH, Catley M, Davey NJ, Kuppuswamy A, Strutton P, Frankel HL, Jamous A, Savic G (2007) Review of physiological motor outcome measures in spinal cord injury using transcranial magnetic stimulation and spinal reflexes. J Rehabil Res Dev 44:69–76

Fouad K, Pedersen V, Schwab ME, Brösamle C (2001) Cervical sprouting of corticospinal fibers after thoracic spinal cord injury accompanies shifts in evoked motor responses. Curr Biol 11:1766–1770

Ghosh A, Haiss F, Sydekum E, Schneider R, Gullo M, Wyss MT, Mueggler T, Baltes C, Rudin M, Weber B, Schwab ME (2010) Rewiring of hindlimb corticospinal neurons after spinal cord injury. Nat Neurosci 13:97–104

Griffiths IR, McCulloch MC (1983) Nerve fibers in spinal cord impact injuries. Part 1. Changes in the myelin sheath during the initial 5 weeks. J Neurol Sci 58:335–349

Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005) Theta burst stimulation of the human motor cortex. Neuron 45:201–206

Kirshblum SC, O'Connor KC (1998) Predicting neurologic recovery in traumatic cervical spinal cord injury. Arch Phys Med Rehabil 79:1456–1466

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501–519

Kumru H, Murillo N, Samso JV, Valls-Sole J, Edwards D, Pelayo R, Valero-Cabre A, Tormos JM, Pascual-Leone A (2010) Reduction of spasticity with repetitive transcranial magnetic stimulation in patients with spinal cord injury. Neurorehabil Neural Repair 24:435–441

Kuppuswamy A, Balasubramaniam AV, Maksimovic R, Mathias CJ, Gall A, Craggs MD, Ellaway PH (2011) Action of 5 Hz repetitive transcranial magnetic stimulation on sensory, motor and autonomic function in human spinal cord injury. Clin Neurophysiol (in press)

Levy WJ Jr, Amassian VE, Traad M, Cadwell J (1990) Focal magnetic coil stimulation reveals motor cortical system reorganized in humans after traumatic quadriplegia. Brain Res 510:130–134

Lissens MA, Vanderstraeten GG (1996) Motor evoked potentials of the respiratory muscles in tetraplegic patients. Spinal Cord 34:673–678

Nielsen JF, Sinkjaer T, Jakobsen J (1996) Treatment of spasticity with repetitive magnetic stimulation: a double-blind placebo-controlled study. Mult Scler 2:227–232

Ortu E, Deriu F, Suppa A, Tolu E, Rothwell JC (2008) Effects of volitional contraction on intracortical inhibition and facilitation in the human motor cortex. J Physiol 586:5147–5159

Perez MA, Lungholt BK, Nielsen JB (2005) Short-term adaptations in spinal cord circuits evoked by repetitive transcranial magnetic stimulation: possible underlying mechanisms. Exp Brain Res 162:201–212

Petersen NT, Pyndt HS, Nielsen JB (2003) Investigating human motor control by transcranial magnetic stimulation. Exp Brain Res 152:1–16

Petersen NC, Butler JE, Taylor JL, Gandevia SC (2010) Probing the corticospinal link between the motor cortex and motoneurones: some neglected aspects of human motor cortical function. Acta Physiol (Oxf) 198:403–416

Quencer RM, Bunge RP, Egnor M, Green BA, Puckett W, Naidich TP, Post MJ, Norenberg M (1992) Acute traumatic central cord syndrome: MRI-pathological correlations. Neuroradiology 34:85–94

Raineteau O, Schwab ME (2001) Plasticity of motor systems after incomplete spinal cord injury. Nat Rev Neurosci 2:263–273

Raineteau O, Fouad K, Bareyre FM, Schwab ME (2002) Reorganization of descending motor tracts in the rat spinal cord. Eur J Neurosci 16:1761–1771

Reis J, Swayne OB, Vandermeeren Y, Camus M, Dimyan MA, Harris-Love M, Perez MA, Ragert P, Rothwell JC, Cohen LG (2008) Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control. J Physiol 586:325–351

Rosenzweig ES, Courtine G, Jindrich DL, Brock JH, Ferguson AR, Strand SC, Nout YS, Roy RR, Miller DM, Beattie MS, Havton LA, Bresnahan JC, Edgerton VR, Tuszynski MH (2010) Extensive spontaneous plasticity of corticospinal projections after primate spinal cord injury. Nat Neurosci 13:1505–1510

Rothwell JC, Hallett M, Berardelli A, Eisen A, Rossini P, Paulus W (1999) Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl 52:97–103

Roy FD, Zewdie ET, Gorassini MA (2011) Short-interval intracortical inhibition with incomplete spinal cord injury. Clin Neurophysiol 122:1387–1395

Saturno E, Bonato C, Miniussi C, Lazzaro V, Callea L (2008) Motor cortex changes in spinal cord injury: a TMS study. Neurol Res 30:1084–1085

Shimizu T, Hino T, Komori T, Hirai S (2000) Loss of the muscle silent period evoked by transcranial magnetic stimulation of the motor cortex in patients with cervical cord lesions. Neurosci Lett 286:199–202

Smith HC, Savic G, Frankel HL, Ellaway PH, Maskill DW, Jamous MA, Davey NJ (2000) Corticospinal function studied over time following incomplete spinal cord injury. Spinal Cord 38:292–300

Thomas SL, Gorassini MA (2005) Increases in corticospinal tract function by treadmill training after incomplete spinal cord injury. J Neurophysiol 94:2844–2855

Topka H, Cohen LG, Cole RA, Hallett M (1991) Reorganization of corticospinal pathways following spinal cord injury. Neurology 1991(41):1276–1283

Totoiu MO, Keirstead HS (2005) Spinal cord injury is accompanied by chronic progressive demyelination. J Comp Neurol 486:373–383

Valero-Cabre A, Oliveri M, Gangitano M, Pascual-Leone A (2001) Modulation of spinal cord excitability by subthreshold repetitive transcranial magnetic stimulation of the primary motor cortex in humans. NeuroReport 12:3845–3848

Valle AC, Dionisio K, Pitskel NB et al (2007) Low and high frequency repetitive transcranial magnetic stimulation for the treatment of spasticity. Dev Med Child Neurol 49:534–538

Vavrek R, Girgis J, Tetzlaff W, Hiebert GW, Fouad K (2006) BDNF promotes connections of corticospinal neurons onto spared descending interneurons in spinal cord injured rats. Brain 129:1534–1545

Weidner N, Ner A, Salimi N, Tuszynski MH (2001) Spontaneous corticospinal axonal plasticity and functional recovery after adult central nervous system injury. Proc Natl Acad Sci U S A 98:3513–3518

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996a) The effect of lorazepam on the motor cortical excitability in man. Exp Brain Res 109:127–135

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996b) Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 40:367–378

Chapter 16
Examining the Cortical Phenomena of Psychiatric Disorders using Transcranial Magnetic Stimulation

Lakshmi N. Ravindran, Natasha Radhu and Zafiris J. Daskalakis

Abstract Transcranial magnetic stimulation (TMS) is used to index several neurophysiological processes including inhibition, excitability, and plasticity to better understand psychiatric illnesses. Assessing such cortical phenomena using TMS provides valuable insights into the neurobiological substrates underlying psychiatric disorders. The purpose of this chapter is to focus on TMS studies which have enhanced our understanding of schizophrenia (SCZ), major depressive disorder (MDD), bipolar disorder (BD), and obsessive–compulsive disorder (OCD). Although the evidence base is still limited, research to date suggests that disorders, such as SCZ, MDD, BD, and OCD are characterized by deficits in cortical inhibition and by abnormalities in cortical excitability. In this chapter, such findings will be reviewed and their importance discussed vis à vis healthy and diseased states. We will conclude by highlighting the limitations of this literature and discuss their potential future applications for the development of biomarkers in psychiatric conditions.

16.1 Introduction

Transcranial magnetic stimulation (TMS) is an important neurophysiological experimental tool that allows researchers to non-invasively study the cortex in healthy individuals and in patients with neuropsychiatric disorders (Barker et al. 1985). TMS can be a useful method to better understand the neurobiology of

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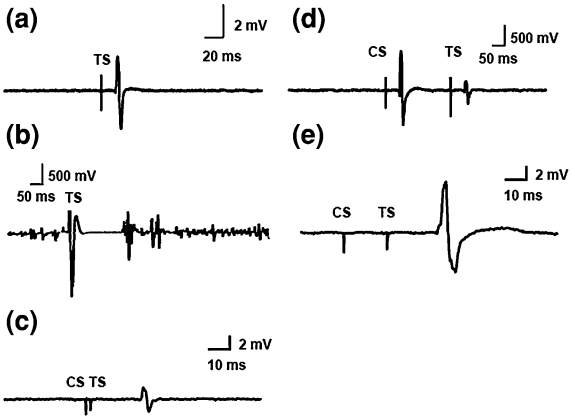

Fig. 16.1 Surface electromyogram recordings from a right hand muscle. **a** A single test stimulus (TS) applied to the left motor cortex producing a motor evoked potential (MEP). **b** The cortical silent period (CSP) induced following a 40 % suprathreshold TS applied to the left motor cortex while the right hand muscle is tonically activated. The CSP starts at the onset of the MEP and ends with the return of motor activity. **c** Short interval cortical inhibition (SICI), a conditioning stimulus (CS) precedes the TS by 2 ms to and inhibits the MEP produced by the TS. **d** Long interval cortical inhibition (LICI), the CS precedes the TS by 100 ms and inhibits the MEP produced by the TS. **e** Intracortical facilitation (ICF), the CS precedes the TS by 20 ms, facilitating the MEP produced by the TS

cognitive function, behavior, and emotional processing (McClintock et al. 2011). It involves the generation of a magnetic field through the use of an electromagnetic coil connected to a TMS device which induces an electrical current in the brain (Wagner et al. 2007). Barker et al. demonstrated that a single TMS pulse applied to the motor cortex could activate cortical tissues associated with the hand or leg muscles and this activation could elicit motor evoked potentials (MEP) at the periphery captured through electromyography (EMG) recordings (Fig. 16.1a) (Barker et al. 1985). TMS is used as an investigational tool as it assesses a variety of cortical phenomena including cortical inhibition (CI), excitation and plasticity (Classen et al. 1998; Kujirai et al. 1993). Assessing such cortical phenomena using TMS provides valuable insights into the neurophysiological substrates underlying psychiatric disorders. This chapter aims to focus on TMS studies which have enhanced our understanding of psychiatric diseases including, schizophrenia (SCZ), major depressive disorder (MDD), bipolar disorder (BD), and obsessive–compulsive disorder (OCD). A literature search was performed using PubMed from 1990 through July 2011, Ovid Medline from 1990 through July 2011, Embase Psychiatry from 1990 through July 2011, and PsycINFO from 1990 through July 2011. The following search terms were used: *transcranial magnetic stimulation, TMS, TMS–EEG, psychiatry, mental disorder, psychiatric disorder, schizophrenia, depression, major depressive disorder, bipolar disorder, mania, obsessive–compulsive disorder, anxiety disorder, cortical inhibition,*

short interval cortical inhibition, long interval cortical inhibition, cortical silent period, resting motor threshold, active motor threshold, cortical excitability, motor evoked potential amplitude, plasticity, paired-associative stimulation, and use-dependent plasticity.

16.2 Schizophrenia

SCZ is a severe mental illness which is characterized by delusions, hallucinations, disorganized thinking, and often life-long disability (van Os and Kapur 2009). SCZ is a debilitating disorder that exacts enormous personal, social, and economic costs (van Os and Kapur 2009). It is estimated that patients with SCZ occupy 10 % of all hospital beds and despite treatment efforts, as many as 15 % of those diagnosed with SCZ eventually commit suicide (Kaplan et al. 1994). Despite some treatment successes, up to 45 % of patients remain treatment resistant (Pantelis and Lambert 2003). This section will review SCZ studies using TMS on the following topics, CI in motor and non-motor regions, plasticity, connectivity, and the neural basis of social functioning.

16.2.1 TMS Paradigms to Assess Cortical Inhibition and Excitation

Abnormalities in CI have been proposed as an important pathophysiologic mechanism in SCZ. CI refers to a neurophysiologic process, whereby γ-amino-butyric acid (GABA) inhibitory interneurons selectively attenuate the activity of other neurons (e.g., pyramidal neurons) in the cortex (Daskalakis et al. 2007). GABAergic interneurons elicit inhibitory postsynaptic potentials (IPSPs) to modify cortical output (Krnjevic 1997). Research suggests evidence for neurophysiological impairments related to GABAergic deficits in SCZ. For example, Benes et al. (1991) first reported that patients with SCZ have morphologic changes in cortical GABA interneurons, by demonstrating a decreased density of non-pyramidal cells (i.e., interneurons) in anterior cingulate layers II-VI and in prefrontal cortex layer II. The above evidence suggests a neurophysiological impairment in SCZ. TMS can be used for further understanding of the neurophysiological mechanisms involved to then develop biological markers and novel treatment approaches in the future. TMS represents a non-invasive method which assesses inhibitory circuits that are mediated, in part, through GABA inhibitory interneurons. These inhibitory paradigms include cortical silent period (CSP), short interval cortical inhibition (SICI), and long interval cortical inhibition (LICI) (Cantello et al. 1992; Kujirai et al. 1993). Studies suggest that CSP and LICI are related to $GABA_B$ receptor-mediated inhibitory neurotransmission (Siebner et al.

1998; Werhahn et al. 1999), whereas, SICI is related to $GABA_A$ receptor-mediated inhibitory neurotransmission (Ziemann et al. 1996). CSP duration (Fig. 16.1b) is obtained in a moderately tonically active muscle (i.e., 20 % of maximum contraction) by stimulating the motor cortex with intensities of 110–160 % of resting motor threshold (RMT). RMT is defined as the minimal intensity that produces a MEP of >50 μV in 5 of 10 trials in a relaxed muscle (Kujirai et al. 1993). CSP duration is measured from MEP onset to the return of any voluntary EMG activity referred to as absolute CSP, ending with a deflection in the EMG waveform (Tergau et al. 1999). In SICI, a subthreshold conditioning stimulus (CS), which is set at 80 % of RMT precedes a suprathreshold test stimulus (TS), which is adjusted to produce an average MEP of 0.5–1.5 millivolt (mV)-peak-to-peak amplitude in the contralateral muscle (Kujirai et al. 1993). To measure SICI conditioning stimuli are applied to the motor cortex before the TS at interstimulus intervals (ISIs) between 1 ms (ms) to 4 ms (Fig. 16.1c). LICI refers to the pairing of a suprathreshold CS followed by a suprathreshold TS at long ISIs (e.g., 100 ms), which inhibits the MEP produced by the TS (Fig. 16.1d) (Claus et al. 1992; Valls-Sole et al. 1992). Another paradigm which measures CI is transcollosal inhibition (TCI) defined as a suprathreshold CS applied to the right motor cortex several ms prior to a suprathreshold TS applied to the left motor cortex which inhibits the size of the MEP produced by the TS by 50–75 %. Stimuli are set to produce MEPs of 0.5–1.5 mV peak to peak amplitude in the contralateral muscle (Ferbert et al. 1992), the CS occurred at about 2, 6, 10, 15, and 20 ms before the TS. A paired pulse paradigm can also be used to examine the phenomenon of cortical excitability through intracortical facilitation (ICF), whereby, conditioning stimuli are applied to the motor cortex before the TS at ISIs usually between 7–20 ms (Fig. 16.1e). It has been shown that ICF originates from excitatory postsynaptic potentials transmitted by N-methyl-D-aspartate (NMDA) glutamate receptors (Nakamura et al. 1997). TMS also permits assessment of RMT which is a global measure of corticospinal excitability and depends on the excitability of axons activated by the TMS pulse, as well as the excitability of synaptic connections at both the cortical and spinal level (Paulus et al. 2008). The RMT depends on glutamatergic synaptic excitability (Paulus et al. 2008). The active motor threshold (AMT) is defined as the lowest intensity that produces an MEP of >100 μV in 5 of 10 trials in a moderately active muscle (Chen et al. 1998b). The AMT is measured during muscle contraction, where corticospinal neurons and spinal motor-neurons are very close to firing threshold (Paulus et al. 2008).

16.2.2 Examining Neurophysiology in Schizophrenia

One of the first neurophysiological studies using TMS to evaluate psychiatric disorders was by Abarbanel et al. (Abarbanel et al. 1996) who studied cortical excitability using TMS in 10 medicated patients with MDD, 10 medicated patients with SCZ, and 10 non-age-or gender-matched healthy control participants as a

comparison group. The dependent variables included total conduction time (calculated from TMS onset to MEP onset), central conduction time (calculated by subtracting peripheral conduction time from total conduction time), MEP ratio (obtained from TMS and peripheral nerve root stimulation), and motor threshold (MT). MEP ratio and MT represent measures of cortical excitability where MT is defined as the minimum intensity of the stimulator output needed to elicit a minimal MEP response in the target muscle. By contrast, MEP size is obtained by stimulating the cortex with intensities above the MT and its size is typically measured by recording peak-to-peak amplitude. This study demonstrated that the MT was lower and MEP amplitudes were larger in SCZ patients compared with MDD patients and healthy controls; the latter two groups did not differ significantly. There were no significant differences in conduction time or left–right differences in MT or MEP amplitude between groups. These findings provided initial evidence for increased cortical excitability in patients with SCZ.

In another early study, Puri et al. (Puri et al. 1996) found that the MEP latency was significantly shorter in unmedicated patients with SCZ compared with healthy age- and gender-matched control participants. In contrast to the findings of Abarbanel et al. (Abarbanel et al. 1996), they found no differences in MT or MEP amplitude. Davey et al. (1997) compared unmedicated SCZ patients to medicated SCZ patients evaluating MT, MEP latency, MEP amplitude, CSP, and EMG suppression for the early and late part of the CSP. They found that medicated patients showed a weaker period of EMG suppression after the MEP and a longer latency to maximum EMG suppression than drug-naïve patients. They did not detect any differences in MT or MEP latency. These earlier studies constitute the first use of TMS as an investigative technique and provide a neurophysiological demonstration of motor CI dysfunction in SCZ.

There are some limitations to consider when comparing results of the earlier studies. For example, a majority of TMS studies examined the neurophysiology of the motor cortex with a figure-of-8 shaped coil, however, Puri et al. (1996) and Davey et al. (1997) applied TMS over the vertex using a circular coil. Furthermore, Abarbanel et al. (1996) examined medicated patients, Puri et al. (1996) examined unmedicated patients and Davey et al. (1997) studied both medicated and unmedicated patients but with no control group. Finally, these three studies had relatively small sample sizes.

Consistent with Abarbanel et al. several studies have since demonstrated decreased MT (i.e., increased cortical excitability) in SCZ. In particular, two studies reported a reduced left hemisphere RMT in unmedicated patients. Daskalakis et al. (Daskalakis et al. 2002b) reported a significantly lower RMT in unmedicated patients compared with medicated patients and healthy controls. There were no differences between medicated patients and healthy controls. These findings are consistent with Eichhammer et al. (Eichhammer et al. 2004) as they reported a lower RMT in drug-naïve first-onset patients with SCZ. However, in contrast, Pascual-Leone et al. (Pascual-Leone et al. 2002) observed a significantly higher RMT (in both left and right hemispheres) in medicated patients compared with unmedicated patients and healthy controls without an RMT difference

between the latter two groups. Furthermore, medicated patients had significantly higher RMT in the left hemisphere than unmedicated patients and controls, whereas controls demonstrated a higher RMT in the right than the left compared to both medicated and unmedicated groups. Additionally, several studies demonstrated no RMT differences between SCZ patients and controls (Bajbouj et al. 2004; Boroojerdi et al. 1999; Daskalakis et al. 2008b; Fitzgerald et al. 2002a; Fitzgerald et al. 2002b; Fitzgerald et al. 2003; Herbsman et al. 2009; Koch et al. 2008; Liu et al. 2009; Oxley et al. 2004; Reid et al. 2002; Wobrock et al. 2009; Wobrock et al. 2008). Many factors may contribute to the inconsistent findings such as, sample size, differing coil types (i.e., circular vs. figure-of-8), illness duration, and treatment with antipsychotic medication.

Additional studies have characterized CI abnormalities in SCZ. For example, Daskalakis et al. (2002a) measured MT, SICI-ICF, CSP and TCI in 15 unmedicated patients with SCZ (14 medication-naïve and 1 medication-free for longer than 1 year), 15 medicated SCZ patients, and 15 healthy controls. They found that unmedicated SCZ patients had significantly lower CI compared with healthy controls in measures of SICI, CSP, and TCI providing TMS evidence for deficient GABAergic neurotransmission in SCZ. Similarly, Pascual-Leone et al. (2002) found that medicated SCZ patients demonstrated significantly decreased SICI (average ISIs of 1, 3, and 4 ms) relative to unmedicated patients and control participants. The difference was more pronounced for the right than the left hemisphere. ICF (average ISIs of 12 and 20 ms) was significantly greater in medicated patients relative to unmedicated patients and healthy controls. The authors concluded striking abnormalities in medicated patients used in this study relative to control and unmedicated patients. Fitzgerald et al. (2002c) evaluated 20 patients with SCZ treated with olanzapine and 20 with risperidone compared to 22 healthy controls. They found significantly higher MT in risperidone patients compared to olanzapine and significantly lower CSP and TCI (reduction in MEP size) in risperidone and olanzapine treated groups versus healthy controls. No differences in SICI were found. Further, Fitzgerald et al. in 2002 (Fitzgerald et al. 2002b) found comparable results in 22 medicated patients with SCZ compared with 21 healthy controls. They demonstrated significantly lower SICI and CSP within SCZ group versus healthy controls. Finally, Fitzgerald et al. (2002a) evaluated TCI in 25 patients with SCZ and 20 healthy controls. Similarly, they demonstrated a significant decrease in TCI in patients independent of medication dose. More recently, Hoy et al. (2008) measured TCI and transcollosal facilitation (TCF) using paired-pulse TMS in 15 medicated SCZ patients and 15 control participants. TCF and TCI involves stimulation of the contralateral motor cortex several ms before stimulation of the ipsilateral motor cortex, inhibiting or enhancing the size of the MEP produced by ipsilateral stimulation as a function of the interval between them (Hanajima et al. 2001). They found that patients with SCZ exhibited significantly less TCI than controls and there was no significant difference in TCF. This finding supports the alterations in CI mechanisms, demonstrated in several previous studies with SCZ patients. In contrast to these findings, five studies measuring TCI (ipsilateral silent period) in patients with SCZ

found that it was significantly longer compared with healthy controls (Bajbouj et al. 2004; Boroojerdi et al. 1999; Fitzgerald et al. 2002a; Fitzgerald et al. 2002c; Hoppner et al. 2001). Taken together, these studies provide evidence to suggest that patients with SCZ show deficits in CI of the motor cortex.

More recent studies also suggest a deficit in CI using TMS in patients with SCZ. For example, Daskalakis et al. (2008b) reported that 10 clozapine treated patients with SCZ had significantly longer CSPs compared with 10 healthy participants and 6 unmedicated SCZ patients. A later study by Liu et al. (2009) with a large sample of 78 SCZ patients and 38 healthy controls confirmed that clozapine treated SCZ patients demonstrated a longer CSP and reduced SICI compared with healthy control participants (Liu et al. 2009). However, patients treated with other antipsychotics and unmedicated patients demonstrated a significantly shorter CSP duration. These findings suggest that CI is involved in the pathophysiology of SCZ and that clozapine may potentiate $GABA_B$ receptor-mediated inhibitory neurotransmission. Across all SCZ patients in this study, CSP was inversely related to negative symptoms, and SICI was inversely associated with positive symptoms, highlighting the role of both $GABA_B$ and $GABA_A$ receptor-mediated inhibitory neurotransmission in SCZ. Also, Wobrock et al. (2008) evaluated CI in 29 medicated SCZ patients compared with 28 healthy controls. They found a significantly reduced SICI in SCZ patients but equivalent ICF in patients and healthy controls. The same group of investigators (Wobrock et al. 2009) subsequently demonstrated a reduced SICI in 29 first episode SCZ patients compared with 44 healthy controls. They found a significant prolongation of the CSP using stimulation intensities of 120 %, 140 %, 160 %, and 180 % of the RMT of the left motor cortex compared to controls. The authors concluded that a reduced SICI in first-episode patients points toward a $GABA_A$ deficit in SCZ while the prolonged CSP could reflect compensatory increased $GABA_B$ neurotransmission induced by the hyperactivity of the dopaminergic system. Consistent with this, Bajbouj et al. (2004) found an increase in the CSP duration with 16 SCZ patients (11 medicated, 5 unmedicated) compared to 16 age- and gender-matched healthy participants. Furthermore, Wobrock et al. (2010) then examined 12 first-episode SCZ patients with a history of comorbid cannabis use and 17 without. They found that patients with a history of comorbid cannabis use had a lower SICI and increased ICF but no significant differences were found in RMT and CSP. Comorbid cannabis abuse was suggested to potentiate the reduced intracortical inhibition and enhanced ICF observed in first episode SCZ patients. This finding is consistent with a previous study, whereby Fitzgerald et al. (2009) also found that heavy and light users of cannabis demonstrated significantly decreased SICI compared to healthy controls. Finally, Soubasi et al. (2010) evaluated 51 medicated SCZ patients and 51 age and sex-matched healthy controls. They measured CSP, RMT, MEP amplitude, MEP latency, and the stimulus intensity to produce a maximum MEP (SI-max) for both the left and right motor cortex. They found a significantly higher RMT, SI-max, CSP, and MEP-latency in patients compared to healthy controls in both left and right motor cortices. In particular, patients treated with ziprasidone demonstrated the highest SI-max for both hemispheres, and the highest RMT for the left

hemisphere, while patients treated with olanzapine demonstrated the lowest RMT for the left hemisphere while patients on quetiapine showed intermediate values. The authors concluded that the observed TMS changes could be interpreted as alterations of intracortical excitability and defects of CI which may be attributed to the illness, antipsychotic medication or the interaction.

TMS has also been used to investigate effects of electroconvulsive therapy (ECT) with SCZ patients. A recent treatment study was conducted using CI measures before and after ECT. Dresler et al. (2010) investigated one patient with severe catatonic SCZ treated with ECT after pharmacological approaches did not result in clinical improvement. They measured SICI (2 ms) and ICF (15 ms) before and after nine sessions of ECT; they found a significant increase in SICI and significant decrease in ICF after ECT complemented with clinical improvements such as, reduced symptoms of catatonia and the enhancement of social competency. These findings suggest that the therapeutic effects of ECT may be related to the potentiation of GABA inhibitory neurotransmission.

LICI refers to the pairing of a suprathreshold CS followed by a suprathreshold TS at long ISIs (e.g., 100 ms), which inhibits the MEP produced by the TS (Fig. 16.1d) (Claus et al. 1992; Valls-Sole et al. 1992). LICI is reportedly optimal at an ISI of 100 ms (Sanger et al. 2001). It is likely that LICI is mediated by slow IPSPs via activation of $GABA_B$ receptors similar to the CSP (Werhahn et al. 1999). In this regard, Fitzgerald et al. (2003) evaluated LICI in 9 medicated and 9 unmedicated patients with SCZ compared with 8 healthy controls. They also evaluated RMT and I-wave facilitation. I-wave facilitation and I-wave production has also been shown to be closely associated with GABAergic inhibition in the motor cortex (Ziemann et al. 1998). Through a modified paired-pulse protocol, I-waves can be recorded from the peripheral hand muscles, I-wave facilitation arises following the presentation of a paired stimulation with a suprathreshold CS followed by stimulation with a subthreshold TS (Ziemann et al. 1998). Both medicated and unmedicated patient groups had significantly enhanced I-wave facilitation than healthy participants, with the effect most prominent in the medicated patients. They found no significant differences between the three groups on measures of LICI or RMT. It was concluded that this study found differences between SCZ patients and healthy participants in I-wave facilitation and these differences were not due to medication due to comparison to an unmedicated group. They suggested that an increase in I-wave facilitation related to a deficit of inhibitory function in SCZ patients and is consistent with previous studies.

16.2.3 Evaluating Cortical Inhibition in Non-Motor Regions

Recently published literature demonstrates that LICI can be measured using a combination of paired-pulse TMS and electroencephalography (EEG) to study how $GABA_B$ receptors modulate oscillations in the brain (Daskalakis et al. 2008c; Fitzgerald et al. 2008) in both the motor cortex and DLPFC with high test–retest

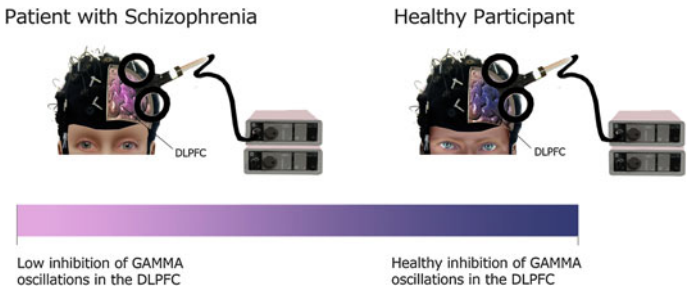

Fig. 16.2 Illustration of combined TMS and EEG applied to the DLPFC. This figure demonstrates that patients with schizophrenia have selective deficits in inhibition of γ oscillations in the DLPFC compared to healthy participants using combined TMS and EEG. (Farzan et al. 2010a)

reliability (Farzan et al. 2010b). LICI using TMS–EEG is defined using the area under rectified unconditioned and conditioned waveforms for the averaged EEG recordings between 50 and 150 ms post-TS. This interval was chosen as it represents the earliest artifact free data (−50 ms post TS) and reflects the duration of $GABA_B$ receptor-mediated IPSPs (−250 ms post CS) (Deisz 1999). Farzan et al. (2010a) demonstrated that overall LICI using TMS-EEG in SCZ patients did not differ significantly in any region compared with BD patients and healthy controls. However, when the evoked EEG response was filtered into different frequency bands, they found a significant deficit in the inhibition of gamma (30–50 Hz) oscillations in the DLPFC of SCZ patients relative to BD patients and healthy controls but no inhibition deficit was found within the motor cortex. The authors concluded that this selective deficit in the inhibition of gamma oscillations demonstrates that the DLPFC is a region in the brain closely related to the pathophysiology of SCZ (Fig. 16.2). An earlier study provided additional support for this finding in SCZ patients compared to healthy controls. For example, Ferrarelli et al. (2008) also demonstrated a decrease in EEG-evoked responses in the gamma band when TMS was applied directly to the frontal cortex, suggesting frontal gamma deficits in SCZ patients.

16.2.4 The Role of Plasticity

Plasticity in the human cortex involves the functional reorganization of synaptic connections in an effort to change or to adapt throughout life. It is characterized by processes involved in learning, memory, and neural repair (Hallett 2000). Evidence suggests that neural plasticity may also be a corollary of CI. That is, the mechanisms mediating plasticity include unmasking existing cortico-cortical connections (Schieber and Hibbard 1993) by removing cortical inhibitory neurotransmission (Jacobs and Donoghue 1991). For example, in humans the

administration of a drug that enhances GABAergic neurotransmission disrupts plasticity (Butefisch et al. 2000). However, plasticity following a lower-limb amputation may occur through reduced cortical GABAergic inhibition (Chen et al. 1998a). Abnormalities in brain plasticity, possibly related to abnormal CI, have been proposed to underlie the pathophysiology of SCZ (Fitzgerald et al. 2004b; Oxley et al. 2004). The following section will review literature on repetitive TMS (rTMS), paired-associative stimulation (PAS), and use-dependent plasticity as TMS studies have been useful in elucidating abnormal plasticity in SCZ.

16.2.5 Repetitive TMS

The application of repeated TMS pulses at a specific rate or frequency is known as rTMS which can be used to modulate cortical plasticity, excitability, and inhibition. Two treatment studies were conducted that assessed CI before and after rTMS treatment sessions with SCZ patients. Fitzgerald et al. (2004b) applied 900 rTMS stimuli with a frequency of 1 Hz and intensity of 110 % of the RMT over the primary motor cortex. It was demonstrated that healthy participants showed an increase in the RMT after rTMS, whereas medicated and unmedicated patients demonstrated an RMT decrease. Furthermore, there was a significant increase in the AMT in healthy participants whereas unmedicated patients demonstrated an AMT decrease. Finally, the CSP was decreased in healthy participants after rTMS, and neither patient group displayed such changes. In a similar study, Oxley et al. (2004) examined changes in TMS measures after rTMS of the supplementary motor cortex in 12 SCZ patients and 12 healthy controls. They found that although there was no difference in RMT between groups at baseline, the patient group had noticeably less CI than the control group at baseline. Following rTMS the change in both MEP size and RMT between groups was significant. After rTMS, MEP size was suppressed in the control group and increased in the patient group, whereas RMT increased in the control group and decreased in the patient group. Patients with SCZ demonstrate abnormal brain responses to rTMS applied to the premotor cortex that appear to relate to reduced motor CI. These findings of abnormal excitability responses to rTMS in SCZ may reflect altered GABA or NMDA receptor-meditated transmission. The above evidence suggests that the decreased neural plasticity is even more pronounced in patients with impaired CI providing additional support for the theory that dysfunctional neural plasticity is a pathophysiological mechanism in SCZ.

16.2.6 Paired-Associative Stimulation

PAS represents a neurophysiologic paradigm that involves peripheral nerve stimulation (PNS) of the median nerve, followed by TMS of the contralateral motor cortex. PAS has been shown to result in long-term potentiation-like activity (PAS-

LTP) if PNS precedes TMS by 25 ms (PAS-25) (Stefan et al. 2000). Rajji et al. (2011) demonstrated MEP potentiation after PAS-25 was associated with enhanced motor learning at 1-week post-PAS in healthy participants. Further, Frantseva et al. (2008) demonstrated that SCZ patients showed deficits in MEP facilitation indicating disrupted LTP-like plasticity associated with impaired motor skill learning compared to healthy participants. This study highlighted the role of PAS–TMS in the motor regions to assess synaptic plasticity in SCZ patients. The authors concluded that patients with SCZ demonstrated impaired LTP-like plasticity which may underlie deficits in learning and memory associated with this illness.

16.2.7 Use-Dependent Plasticity

Use-dependent plasticity is a TMS paradigm which can measure neural plasticity in the cortex (Classen et al. 1998). Use-dependent plasticity is measured through the following tasks. The spontaneous direction of TMS-induced thumb movements are measured in two axes (x and y). Individuals are then trained to perform a simple motor task opposite to the direction of TMS-induced thumb movement. TMS is reapplied to the cortex while evaluating the direction of induced thumb movement, and directional changes in thumb movements are evaluated over time. Classen et al. (1998) found that immediately after training, the direction of TMS-induced movements followed the direction of training. Both GABA and NMDA receptor-mediated neurotransmission play an important role in use-dependent plasticity (Butefisch et al. 2000).

Daskalakis et al. (2008a) evaluated use-dependent plasticity in 14 medicated and six unmedicated patients with SCZ compared with 12 healthy participants. A significant reduction of use-dependent plasticity was demonstrated in SCZ compared with healthy participants. That is, SCZ patients demonstrated significantly small angular deviations in the 5–10 min post-training period versus pretraining compared with controls. The authors concluded that such abnormalities may be related to dysfunctional neurophysiological brain processes, including LTP, that exist as a result of disturbances of GABA, NMDA, and dopamine neurotransmission. These findings potentially account for the aberrant motor performance demonstrated in SCZ. Taken together, these studies provide preliminary evidence for a diminution of the neurophysiological process that mediate neural plasticity in SCZ. The evidence suggests that the decreased neural plasticity is even more pronounced in patients with impaired CI.

16.2.8 Exploring the Disconnection Hypothesis

Current pathophysiological theories of SCZ emphasize the role of altered brain connectivity (Friston 1998; Stephan et al. 2006). This disconnectivity may manifest anatomically, through structural changes of association fibers at the cellular

level, and/or functionally, through aberrant control of synaptic plasticity at the synaptic level (Stephan et al. 2006). Recently, Koch et al. (2008) examined the connectivity between posterior parietal cortex (PPC) and motor cortex in SCZ patients using a new method with paired pulse TMS. A CS was applied to the PPC adjusted to be either suprathreshold (110 % RMT) or subthreshold (90 % RMT) and the TS was set to 1 mV peak to peak at the motor cortex. ISIs were 2, 4, 6, 8, 10, and 15 ms. They demonstrated that when a CS was applied to the PPC in healthy participants, excitability of the ipsilateral motor cortex was increased; however, medicated and unmedicated patients with SCZ failed to show any facilitatory parieto-motor interaction, suggesting a cortico-cortical disconnection in SCZ. Additionally, to study connectivity in the brain, Herbsman et al. (2009) combined TMS with neuroimaging tools such as, magnetic imaging resonance and diffusion tensor imaging in 12 SCZ patients and 5 healthy controls. They found that the anterior-posterior trajectory of the corticospinal tract and the skull-to-cortex distance were highly correlated with MT, while fractional anisotropy, age and SCZ status were not. The skull-to-cortex distance and the anterior component of the corticospinal tract were highly predictive of MT in a linear regression model, and accounted for 82 % of the variance observed ($R^2 = 0.82$, $P < 0.0001$) and the corticospinal tract's anterior–posterior direction alone contributed 13 % of the variance explained. Finally, Voineskos et al. (2010) evaluated TMS-evoked potentials using single-pulse TMS and studied its effects on interhemispherically homologus regions in healthy participants. They found an inverse relationship between microstructural integrity of callosal motor fibers with TMS-induced interhemispheric signal propagation (ISP) from left-to-right motor cortex. Also, they demonstrated an inverse relationship between microstructural integrity of the fibers of the genu of the corpus callosum and TMS-induced ISP from left-to-right DLPFC. These findings support a role for the corpus callosum in preservation of functional asymmetry between homologous cortical regions in healthy participants. The authors concluded that delineation of the relationship between corpus callosum microstructure and ISP in neuropsychiatric disorders, such as SCZ, may reveal a novel neurobiological mechanism of pathophysiology. Taken together, these studies above provide evidence for the abnormal functional integration of neuronal systems associated with SCZ.

16.2.9 Investigating the Neural Basis of Social Functioning

Enticott et al. (2008) used TMS to investigate the neural basis of social cognitive functioning in SCZ, as this phenomenon is not well understood in this population. Recent theoretical accounts propose a central role for the mirror neuron system in social cognition. Mirror neurons become active during both the action and observation of an activity. Fifteen SCZ or schizoaffective medicated patients and 15 healthy controls participated. Measurements included MEP amplitude (120 % of RMT) at baseline and in combination with presenting emotionally neutral visual

stimuli (demonstrating motor activity) such as, a lateral thumb movement, a pen grasp, or handwriting. No baseline between-group difference was observed in MEP amplitude. However, individuals with SCZ or schizoaffective disorder showed reduced MEP facilitation during the observation of action within the stimulated muscle, whereas healthy controls demonstrated a significant increase in MEP amplitude for all conditions. The authors suggested that the absent facilitatory effect may be due to a reduced mirror neuron activity in the premotor cortices of patients with SCZ or schizoaffective disorder. This study highlights the neurophysiological mechanisms associated with abnormal intracortical motor excitatory activity and deficits in CI which may be related to SCZ and the effects of antipsychotic medication.

CI may represent an important neurophysiologic mechanism responsible for the symptoms observed in patients with SCZ. Taken together, an extensive amount of evidence has been generated to support the use of TMS as a measurement of cortical function and as a treatment of psychiatric symptomatology. Future studies are necessary to advance current knowledge by identifying biological markers of both illness and treatment response to developing a deeper understanding of the neurophysiological mechanisms underlying SCZ.

16.3 Major Depressive Disorder

MDD is one of the most prevalent psychiatric disorders, and is estimated to affect 16.6 % of individuals in their lifetime (Kessler et al. 2005). It not only affects physical and cognitive functions but also has a profound impact on psychosocial well-being (Kessler et al. 2005). A number of therapeutic tools, including both medications and psychotherapy, have been developed to treat this disorder, but our understanding of its biological underpinnings remains incomplete. However, burgeoning evidence from different investigational modalities, including TMS, suggest depression may be associated with abnormalities in cortical excitability, and more specifically deficits in CI processes. This evidence is reviewed below.

Early studies focused on post-exercise effects on MEP amplitude. For example, neurophysiological evidence suggests that after a period of muscle activation, MEP amplitudes in healthy controls increase (termed "post-exercise MEP facilitation") for a period of time before eventually, decreasing back to baseline. However, if activation continues to the point of fatigue, MEP amplitudes are observed to then decrease (termed "post-exercise MEP depression") (Samii et al. 1996b). Speculating that because depressed patients complain of overall levels of lower energy and fatigue, there may be an underlying neurophysiological explanation, Samii et al. (1996a) examined the above phenomena in three unmedicated populations: MDD, chronic fatigue syndrome (CFS), and healthy participants. Both clinical populations had impairments in post-exercise MEP facilitation. While CFS subjects had the greatest degree of impairment, the authors reported that MDD patients showed MEP responses that were initially within normal range

but which then decayed faster than normal. Using a similar experimental paradigm, Shajahan et al. (1999a) found medicated MDD patients had overall lower MEP amplitudes during post-exercise facilitation compared to healthy participants (131 % vs. 211 %) and further showed that in MDD subjects the initial facilitation was brief and quickly followed by amplitudes returning to baseline levels. This evidence suggests that MDD was associated with an earlier and greater degree of post-exercise depression. They concluded that these findings pointed to localized deficits in motor cortex excitability in depressed individuals. To examine whether this impairment in post-exercise facilitation was a reflection of disease state, Shahjahan and colleagues (1999b) subsequently examined the phenomena in three specific groups: medicated depressed, medicated euthymic, and healthy controls. They were able to demonstrate that post-exercise MEP facilitation was similar in euthymic and control participants but significantly reduced in the actively depressed group, suggesting that the impaired facilitation observed in depressed individuals is reversible with recovery. Exploring whether these findings were unique to depression or more generalizable to other psychiatric conditions, Reid et al. (2002) used the paradigm to evaluate differences between individuals with MDD, SCZ (both groups medicated), and control participants. They found that both clinical groups had decreased facilitation compared to the control group suggesting that reduced post-exercise facilitation may be a feature of both MDD and SCZ, each of which have motor function abnormalities as part of their symptom spectrum. Among the limitations of the study, it should be noted that there were significant baseline differences in the three groups with respect to age and gender composition.

Subsequent studies of TMS in MDD have explored a greater variety of neurophysiologic parameters in an attempt to characterize differences between clinical and healthy populations. RMT, a commonly evaluated TMS parameter, is thought to reflect membrane excitability of cortical motor neurons (Ziemann et al. 1996). Potential differences in RMT have been investigated between healthy and MDD populations. For example, in one early study that compared 19 MDD patients and 13 healthy subjects, Grunhaus et al. (2003) failed to find differences in baseline RMT between groups.

Several studies subsequently examined laterality differences in a variety of TMS parameters, including RMT. These studies were initially predicated on findings from imaging studies suggesting hemispheric asymmetries in individuals suffering from MDD (Baxter et al. 1989; Abou-Saleh et al. 1999; Bench et al. 1992). TMS findings of laterality in depression are mixed. In an early study, Maeda et al. (2000) found that individuals with MDD ($N = 8$) had significantly higher RMT on the left hemisphere compared to the right whereas the converse was true for healthy controls ($N = 8$). Using paired-pulse TMS they were also able to show greater right sided but lower left sided motor cortex excitability, as measured by SICI and ICF at an ISI of 6 ms, in MDD subjects compared to healthy participants. In line with this, Bajbouj et al. (2006b) detected a lower RMT in the right hemisphere of 20 unmedicated MDD subjects versus matched controls, but were unable to detect group differences in RMT on the left. They also found

evidence of deficient CI in MDD subjects noting that, although no laterality differences were found, overall CSP duration was significantly shorter and SICI decreased in the clinical population, suggesting deficits in both $GABA_A$ and $GABA_B$ neurotransmission are implicated in MDD. Similarly, Lefaucheur and colleagues (Lefaucheur et al. 2008) found that depressed individuals had increased RMT on the left compared to the right, both within the group ($N = 35$) and compared to healthy individuals ($N = 35$), but after statistical correction the differences were no longer significant. Within the MDD group, CSP was shorter and SICI and ICF were both decreased on the left side, but only the latter two measures remained significant after correction; no hemispheric asymmetry was seen within the healthy group. When these measures were compared directly between the two groups CSP was shorter in the left hemisphere and SICI reduced bilaterally in MDD subjects. These results suggest that depression is associated with abnormalities in both glutamatergic and GABAergic pathways, particularly in the left hemisphere.

Levinson et al. (2010) examined CI in 25 medicated individuals with treatment resistant depression (TRD), 19 medicated euthymic subjects, 16 unmedicated depressed patients, and 25 healthy controls. RMT was found to be significantly higher in the left motor cortex of the TRD group compared to the other three subgroups. Similar to the studies above, the investigators found that CSP was significantly longer in control participants compared to all three depressed populations, but no differences in CSP were detected between depressed subgroups. In contrast, SICI was significantly reduced only in the TRD population. The findings above all held true after controlling for benzodiazepine use which has been shown to affect TMS parameters. Since all MDD patients showed CSP abnormalities but only TRD subjects additionally demonstrated SICI reductions, the authors concluded that the depressed state may be overall associated with $GABA_B$ deficits. However, severe symptomatology, as seen in TRD, may be associated with greater deficits in GABAergic neurotransmission such that both $GABA_A$ and $GABA_B$ are affected.

These findings of RMT in the four studies above suggest decreased cortical excitability of the left hemisphere. Fitzgerald et al. (2004a) investigated laterality differences in cortical excitability of 60 subjects with TRD. In contrast to the studies above, they detected a trend for lower RMT in the left hemisphere ($p = 0.09$), but did not include a control group for comparison. No laterality differences were found for CSP or ICF. Consistent with earlier studies finding decreased excitability of the left hemisphere, SICI was significantly less on the right side at an ISI of 1 ms; however, this difference was not present at an ISI of 3 ms. Finally, a more recent study by Navarro et al. (2009) failed to detect hemispheric asymmetry in RMT within their sample of 91 MDD patients, but similarly did not have a comparison group. However, they found that benzodiazepine use was associated with greater RMT bilaterally.

In addition to trying to assess baseline differences between populations, researchers have also explored whether therapeutic interventions can affect TMS measures. In 12 depressed subjects who received a single right unilateral ECT

treatment, no effect was seen on RMT (Bajbouj et al. 2003). However, ECT was associated with prolonged post-excitatory inhibition as well as increased SICI but decreased ICF, all of which suggested that ECT facilitates an increase in inhibitory transmission, thus providing support for the idea that GABAergic mechanisms may underlie the therapeutic effects of ECT. This investigation was extended when 10 MDD subjects, medicated with either venlafaxine or tranylcypromine, received 10 right unilateral ECT treatments; cortical parameters were measured pre- and post- treatments (Bajbouj et al. 2006a). As previously, no changes were seen in RMT while CSP duration and SICI were both increased. However, in this study, ICF remained unchanged following repeated ECT. The findings provided further evidence to support the idea that ECT induces its therapeutic benefit though changes in both $GABA_A$ and $GABA_B$ neurotransmission.

Changes in cortical excitability following treatment with rTMS have also been explored. Christayakov and colleagues (2005a) randomized 59 medication-free depressed inpatients to 2 weeks of left or right rTMS to the prefrontal cortex, each provided at either low or high frequencies (3 Hz and 10 Hz) and compared results of these four groups to those obtained with clomipramine treatment (150 mg daily). Following treatment, an increased RMT was found but only in the two groups assigned to high frequency (10 Hz) rTMS. The other measured parameter, CSP, was not affected by any of the five treatments. The same investigators then examined cortical excitability changes in MDD subjects derived from either bilateral ECT or sham rTMS ($N = 10$) or combined ECT and rTMS ($N = 12$) to the right prefrontal cortex over 3 weeks (Chistyakov et al. 2005b). Overall clinical improvement did not differ between groups, but when the groups were combined for analysis responders showed decreased AMT and reduced SICI on the left. The authors speculated that ECT and rTMS might function to restore impaired excitability in the left hemisphere of depressed individuals. By contrast, the effects of rTMS on RMT was explored in 50 antidepressant-free MDD individuals and no overall effect was seen even after controlling for age and benzodiazepine use (Zarkowski et al. 2009). However, it should be noted that the number of rTMS treatments provided to subjects was variable since the dataset was part of a larger sham-controlled rTMS trial.

Many of the above trials have included subjects already on psychotropic agents. However, it is necessary to parse out whether the phenomena observed are related to disease state or to medication effects, and ideally how different classes of medications may affect cortical excitability in depressed individuals. Manganotti and colleagues (Manganotti et al. 2001) administered a single dose of 25 mg intravenous (IV) clomipramine in six medication-free depressed subjects with measures taken before and at 4, 8, and 24 h after administration. Drug administration resulted in significant increases in SICI, RMT, and AMT at 4 h which were rendered non-significant by 8 h. By contrast, ICF was significantly decreased at 4 h but no longer at 8 h. These temporary but significant effects of clomipramine on both SICI and ICF suggest that it works by effecting changes in both GABA and glutamate cortical transmission respectively. The authors speculated that the motor threshold effects could be due to clomipramine-induced changes in neuronal

membrane excitability but could not exclude the possibility that the sedating qualities of clomipramine could also have affected these measures which have been shown to be increased by drowsiness (Rossini et al. 1994).

More recently, Minelli et al. (2010) attempted to replicate and expand the above results in a randomized placebo-controlled trial comparing the effects of two IV antidepressants, clomipramine, and citalopram in 30 unmedicated subjects with TRD. TMS parameters were measured pre-drug administration and at 3.5, 8, and 12 h afterward. The two groups that received active drugs had significant increases in RMT at 3.5 h but the effect disappeared by 8 h in the citalopram group. Clomipramine was also found to enhance SICI, even at the 8 h mark, but citalopram effects on SICI were only observed at the trend level ($p = 0.057$) by 8 h. By contrast, both drugs showed significant decreases in ICF at 3.5 h although these effects were no longer present at 8 h. No changes in TMS measures were seen at any time point within the placebo group. The authors concluded that both IV citalopram and clomipramine produced temporary but noteworthy suppression of cortical excitability in subjects with TRD, as measured by changes in RMT, SICI, and ICF, with slightly more prolonged effects favoring clomipramine.

Cortical excitability effects of mirtazapine, an antidepressant which enhances both serotonin and norepinephrine neurotransmission, were investigated by Munchau et al. (2005). They administered a single oral dose of 30 mg to subjects with a primary diagnosis of epilepsy and comorbid major depression ($N = 7$), all on at least one antiepileptic drug, and to healthy controls ($N = 6$). Measures were taken before and 24 h after drug administration. Depressed patients were then provided a further 3 weeks of mirtazapine therapy at the same dose at which time measures were repeated. At baseline, patients were observed to have significantly greater RMT, AMT, and ratio of CSP duration to MEP area. In patients, a single dose of mirtazapine was associated with a reduction in AMT but not RMT at 24 h, but had no effect on CSP duration or MEP area, even after 3 weeks of treatment. However, in control participants, mirtazapine was not associated with any effect on AMT or RMT but did result in a significantly longer CSP and a trend toward increased MEP amplitude ($p = 0.076$). Neither SICI nor ICF were different between groups either before or after medication. Based on the findings, the authors suggested that, in both populations, mirtazapine enhances excitability of pyramidal tract neurons in an activated state (muscles voluntarily contracted) as a result of its actions on noradrenaline and/or serotonin.

Taken together, these findings suggest that MDD is associated with deficits in GABAergic inhibitory neurotransmission and abnormalities in excitatory functions in the motor cortex. Future studies are needed to explore regions of the cortex that are more closely associated with the pathophysiology of this disorder (i.e., the DLPFC) before and after medication or brain stimulation treatments to determine whether changes in CI are mechanistically related to treatment response.

16.4 Bipolar Disorder

BD is a serious neuropsychiatric illness with prevalence estimates of 2.4 % worldwide (Merikangas et al. 2011). It is characterized by periods of mania or hypomania alternating with phases of depression (Benazzi 2007) and is associated with an early age of onset, usually between 16 to 26 years (Javaid et al. 2011; Manchia et al. 2008). Suicide and suicide attempts are significant contributors to premature mortality and disability within this mental illness (Goodwin et al. 2003). Despite these sobering statistics, relatively little work has been done to understand the neurophysiological underpinnings of this disease. Limited neuroanatomical evidence suggests that BD patients have impaired cortical inhibitory neurotransmission (Benes et al. 1998). Benes and Berretta found that the density of cortical GABA interneurons, which mediate CI, is reduced in the anterior cingulate cortex among patients with BD (Benes and Berretta 2001) and also found a 30 % decrease in cortical inhibitory GABAergic interneurons in BD, compared with a 16 % decrease in patients with SCZ (Benes and Berretta 2001). The data suggests a loss of GABAergic interneurons in both BD and SCZ. However, there is little in vivo neurophysiological evidence supporting such impairments in BD. Levinson et al. (2007) used TMS to evaluate SICI, CSP, and IHI in 15 BD patients (13 medicated with a single mood stabilizer and two unmedicated) compared to 15 healthy controls. Their results demonstrated that BD patients demonstrated significant deficits in SICI, CSP and IHI compared with healthy volunteers. It was concluded that GABAergic inhibitory neurotransmission is deficient in the cortex of patients with BD. Furthermore, a majority of patients were medicated; the evidence suggests that these inhibitory deficits are attenuated with treatment. Additional studies are needed with an unmedicated sample and with larger sample sizes as it would be anticipated that the inhibitory deficits would be magnified in the absence of these medications.

16.5 Obsessive–Compulsive Disorder

Estimated to affect up to 2.5 % of the world's population (Karno et al. 1988; Kessler et al. 2005), OCD is a serious mental illness characterized by the presence of recurrent, intrusive and thoughts, impulses or images (obsessions) that are often also accompanied by repetitive rituals or Behaviors designed to counteract the associated anxiety. As obsessive thoughts and/or rituals may cause great distress and take up significant time during the day, OCD often leads to pronounced psychosocial impairment (Eisen et al. 2006). Although its pathophysiology remains to be fully elucidated, it has been speculated to involve inhibitory deficits in orbitofrontal striatal circuits (Menzies et al. 2008).

Several neuroimaging and genetic studies of OCD have been published to date, but TMS studies of OCD are limited. One preliminary study found decreased SICI

in patients with OCD without a history of either comorbid tic's or Tourette's syndrome compared to controls (Greenberg et al. 1998), implicating a role for $GABA_A$ receptor-mediated inhibitory neurotransmission in OCD. These results were expanded when they compared 16 individuals with OCD ($N = 9$ medicated) to 11 healthy participants (Greenberg et al. 2000). In this case, both RMT and AMT were found to be significantly lower in OCD patients compared to controls. Similarly, SICI was lower in OCD patients relative to controls and this difference remained significant even when the same comparison was made using only unmedicated OCD patients; no differences were found for SICI between unmedicated and medicated OCD patients. By contrast, there were no differences in ICF or CSP detected between patient and control groups. When the OCD group was subdivided into those with comorbid tics ($N = 5$) and those without ($N = 11$), the former group was associated with a greater degree of SICI. The authors concluded that OCD, in the presence or absence of comorbid tics, was characterized by deficient SICI, and that although both tic-related and non-tic related OCD might have some common pathophysiology they could still be distinguished.

More recently, Richter et al. (2012) also tried to characterize TMS parameters in a larger sample of OCD patients. They compared 34 patients ($N = 23$ medicated) to 34 healthy individuals. In contrast to the previous study, no overall difference was found in RMT between OCD and healthy groups. However, RMT was significantly lower in the medicated compared to the unmedicated OCD population. Furthermore, CSP was also found to be noticeably shorter in OCD but no further differences were detected between the OCD subgroups. Finally, although this study failed to detect differences in SICI between OCD and healthy individuals, OCD subjects were found to have a significantly greater ICF, regardless of medication status. No correlations were found between illness severity and TMS parameters in either medicated or unmedicated OCD populations. In this case, the results suggest that OCD is associated with deficient CSP and excessive ICF, regardless of medicated state, reflecting abnormalities in $GABA_B$, and NMDA-mediated neurotransmission. The authors suggested that differences between their results and those previously published could be due to the greater number of unmedicated OCD patients and their elevated symptom severity or to the different TMS stimulation intensities used. The discrepant findings in the limited number of studies highlight the need for further research to better characterize the potential abnormalities seen in OCD.

16.6 Conclusions and Future Directions

In summary, TMS is a powerful tool that allows researchers to investigate cortical phenomena in both motor and non-motor regions to better understand the pathophysiology of psychiatric disorders. Although the evidence is still limited, research to date suggests that disorders, such as SCZ, MDD, BD, and OCD are characterized by abnormalities in cortical excitability with particular deficits in CI.

However, the published studies are not entirely consistent. Factors that may play a role in the discrepant results and limit ability to make comparisons include small sample sizes, differences in TMS parameters used, use of heterogeneous populations, and presence of comorbid illness. Further, medications may affect outcomes of TMS measures and it is likely that different classes of psychotropics may do this in unique ways. As such, the inclusion of medicated individuals on various classes of psychotropic agents in these studies is a significant confounder of results. Addressing these issues systematically in future research would allow greater confidence in results and provide a more stable evidence base for elucidating biological markers and mechanisms involved in psychiatric illnesses. In future, the ability to evaluate physiological response profiles of different oscillatory frequencies in response to TMS (combined with EEG) may ultimately serve as key neurophysiological features of psychiatric illness. In conclusion, TMS and EEG will continue to provide a deeper insight into the neurobiological underpinnings of psychiatric disorders. Future research is needed to identify biological markers for the facilitation of early identification of illness and targeted treatment approaches.

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References

Abarbanel JM, Lemberg T, Yaroslavski U, Grisaru N, Belmaker RH (1996) Electrophysiological responses to transcranial magnetic stimulation in depression and schizophrenia. Biol Psychiatry 40(2):148–150. doi: 0006322395006648 [pii]

Abou-Saleh MT, Al Suhaili AR, Karim L, Prais V, Hamdi E (1999) Single photon emission tomography with 99 m Tc-HMPAO in Arab patients with depression. J Affect Disord 55(2–3):115–123

Bajbouj M, Gallinat J, Lang UE, Neu P, Niehaus L (2003) Motorcortical excitability after electroconvulsive therapy in patients with major depressive disorder. Suppl Clin Neurophysiol 56:433–440

Bajbouj M, Gallinat J, Niehaus L, Lang UE, Roricht S, Meyer BU (2004) Abnormalities of inhibitory neuronal mechanisms in the motor cortex of patients with schizophrenia. Pharmacopsychiatry 37(2):74–80. doi: 10.1055/s-2004-815529

Bajbouj M, Lang UE, Niehaus L, Hellen FE, Heuser I, Neu P (2006a) Effects of right unilateral electroconvulsive therapy on motor cortical excitability in depressive patients. J Psychiatr Res 40(4):322–327. doi: S0022-3956(05)00086-5 [pii] 10.1016/j.jpsychires.2005.07.002

Bajbouj M, Lisanby SH, Lang UE, Danker-Hopfe H, Heuser I, Neu P (2006b) Evidence for impaired cortical inhibition in patients with unipolar major depression. Biol Psychiatry 59(5):395–400. doi: S0006-3223(05)00925-X [pii] 10.1016/j.biopsych.2005.07.036

Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. Lancet 1(8437):1106–1107. doi: S0140-6736(85)92413-4 [pii]

Baxter LR Jr, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM (1989) Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 46(3):243–250

Benazzi F (2007) Bipolar disorder–focus on bipolar II disorder and mixed depression. Lancet 369(9565):935–945. doi: S0140-6736(07)60453-X [pii] 10.1016/S0140-6736(07)60453-X

Bench CJ, Friston KJ, Brown RG, Scott LC, Frackowiak RS, Dolan RJ (1992) The anatomy of melancholia–focal abnormalities of cerebral blood flow in major depression. Psychol Med 22(3):607–615

Benes FM, Berretta S (2001) GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. Neuropsychopharmacology 25(1):1–27. doi: S0893-133X(01)00225-1 [pii] 10.1016/S0893-133X(01)00225-1

Benes FM, Kwok EW, Vincent SL, Todtenkopf MS (1998) A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. Biol Psychiatry 44(2):88–97. doi: S0006-3223(98)00138-3 [pii]

Benes FM, McSparren J, Bird ED, SanGiovanni JP, Vincent SL (1991) Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients. Arch Gen Psychiatry 48(11):996–1001

Boroojerdi B, Topper R, Foltys H, Meincke U (1999) Transcallosal inhibition and motor conduction studies in patients with schizophrenia using transcranial magnetic stimulation. Br J Psychiatry 175:375–379

Butefisch CM, Davis BC, Wise SP, Sawaki L, Kopylev L, Classen J, Cohen LG (2000) Mechanisms of use-dependent plasticity in the human motor cortex. Proc Natl Acad Sci U S A 97(7):3661–3665. doi: 10.1073/pnas.050350297050350297 [pii]

Cantello R, Gianelli M, Civardi C, Mutani R (1992) Magnetic brain stimulation: the silent period after the motor evoked potential. Neurology 42(10):1951–1959

Chen R, Corwell B, Yaseen Z, Hallett M, Cohen LG (1998a) Mechanisms of cortical reorganization in lower-limb amputees. J Neurosci 18(9):3443–3450

Chen R, Tam A, Butefisch C, Corwell B, Ziemann U, Rothwell JC, Cohen LG (1998b) Intracortical inhibition and facilitation in different representations of the human motor cortex. J Neurophysiol 80(6):2870–2881

Chistyakov AV, Kaplan B, Rubichek O, Kreinin I, Koren D, Feinsod M, Klein E (2005a) Antidepressant effects of different schedules of repetitive transcranial magnetic stimulation vs. clomipramine in patients with major depression: relationship to changes in cortical excitability. Int J Neuropsychopharmacol 8(2):223–233. doi: S1461145704004912 [pii] 10.1017/S1461145704004912

Chistyakov AV, Kaplan B, Rubichek O, Kreinin I, Koren D, Hafner H, Feinsod M, Klein E (2005b) Effect of electroconvulsive therapy on cortical excitability in patients with major depression: a transcranial magnetic stimulation study. Clin Neurophysiol 116(2):386–392. doi: S1388-2457(04)00366-9 [pii] 10.1016/j.clinph.2004.09.008

Classen J, Liepert J, Wise SP, Hallett M, Cohen LG (1998) Rapid plasticity of human cortical movement representation induced by practice. J Neurophysiol 79(2):1117–1123

Claus D, Weis M, Jahnke U, Plewe A, Brunholzl C (1992) Corticospinal conduction studied with magnetic double stimulation in the intact human. J Neurol Sci 111(2):180–188

Daskalakis ZJ, Christensen BK, Chen R, Fitzgerald PB, Zipursky RB, Kapur S (2002a) Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. Arch Gen Psychiatry 59(4):347–354. doi: yoa01005 [pii]

Daskalakis ZJ, Christensen BK, Fitzgerald PB, Chen R (2008a) Dysfunctional neural plasticity in patients with schizophrenia. Arch Gen Psychiatry 65(4):378–385. doi: 65/4/378 [pii] 10.1001/archpsyc.65.4.378

Daskalakis ZJ, Christensen BK, Fitzgerald PB, Moller B, Fountain SI, Chen R (2008b) Increased cortical inhibition in persons with schizophrenia treated with clozapine. J Psychopharmacol 22(2):203–209. doi: 0269881107084002 [pii] 10.1177/0269881107084002

Daskalakis ZJ, Christensen BK, Fitzgerald PB, Roshan L, Chen R (2002b) The mechanisms of interhemispheric inhibition in the human motor cortex. J Physiol 543(Pt 1):317–326. doi: PHY_017673 [pii]

Daskalakis ZJ, Farzan F, Barr MS, Maller JJ, Chen R, Fitzgerald PB (2008c) Long-interval cortical inhibition from the dorsolateral prefrontal cortex: a TMS-EEG study. Neuropsychopharmacology 33(12):2860–2869. doi: npp200822 [pii] 10.1038/npp.2008.22

Daskalakis ZJ, Fitzgerald PB, Christensen BK (2007) The role of cortical inhibition in the pathophysiology and treatment of schizophrenia. Brain Res Rev 56(2):427–442. doi: S0165-0173(07)00195-6 [pii] 10.1016/j.brainresrev.2007.09.006

Davey NJ, Puri BK, Lewis HS, Lewis SW, Ellaway PH (1997) Effects of antipsychotic medication on electromyographic responses to transcranial magnetic stimulation of the motor cortex in schizophrenia. J Neurol Neurosurg Psychiatry 63(4):468–473

Deisz RA (1999) GABA(B) receptor-mediated effects in human and rat neocortical neurones in vitro. Neuropharmacology 38(11):1755–1766. doi: S0028390899001367 [pii]

Dresler T, Giani AS, Reinsberger C, Scheuerpflug P, Stober G, Fallgatter AJ (2010) Electroconvulsive therapy resolves cortical inhibition and manneristic omissions in a chronic catatonic patient. J Neural Transm 117(10):1209–1212. doi: 10.1007/s00702-010-0467-7

Eichhammer P, Wiegand R, Kharraz A, Langguth B, Binder H, Hajak G (2004) Cortical excitability in neuroleptic-naive first-episode schizophrenic patients. Schizophr Res 67(2–3):253–259. doi: 10.1016/S0920-9964(03)00223-8 S0920996403002238 [pii]

Eisen JL, Mancebo MA, Pinto A, Coles ME, Pagano ME, Stout R, Rasmussen SA (2006) Impact of obsessive-compulsive disorder on quality of life. Compr Psychiatry 47(4):270–275. doi: S0010-440X(05)00151-3 [pii] 10.1016/j.comppsych.2005.11.006

Enticott PG, Hoy KE, Herring SE, Johnston PJ, Daskalakis ZJ, Fitzgerald PB (2008) Reduced motor facilitation during action observation in schizophrenia: a mirror neuron deficit? Schizophr Res 102(1–3):116–121. doi: S0920-9964(08)00167-9 [pii] 10.1016/j.schres.2008.04.001

Farzan F, Barr MS, Levinson AJ, Chen R, Wong W, Fitzgerald PB, Daskalakis ZJ (2010a) Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. Brain 133(Pt 5):1505–1514. doi: awq046 [pii] 10.1093/brain/awq046

Farzan F, Barr MS, Levinson AJ, Chen R, Wong W, Fitzgerald PB, Daskalakis ZJ (2010b) Reliability of long-interval cortical inhibition in healthy human subjects: a TMS-EEG study. J Neurophysiol 104(3):1339–1346. doi: jn.00279.2010 [pii] 10.1152/jn.00279.2010

Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD (1992) Interhemispheric inhibition of the human motor cortex. J Physiol 453:525–546

Ferrarelli F, Massimini M, Peterson MJ, Riedner BA, Lazar M, Murphy MJ, Huber R, Rosanova M, Alexander AL, Kalin N, Tononi G (2008) Reduced evoked gamma oscillations in the frontal cortex in schizophrenia patients: a TMS/EEG study. Am J Psychiatry 165(8):996–1005. doi: appi.ajp.2008.07111733 [pii] 10.1176/appi.ajp.2008.07111733

Fitzgerald PB, Brown TL, Daskalakis ZJ, deCastella A, Kulkarni J (2002a) A study of transcallosal inhibition in schizophrenia using transcranial magnetic stimulation. Schizophr Res 56(3):199–209. doi: S0920996401002225 [pii]

Fitzgerald PB, Brown TL, Daskalakis ZJ, Kulkarni J (2002b) A transcranial magnetic stimulation study of inhibitory deficits in the motor cortex in patients with schizophrenia. Psychiatry Res 114(1):11–22. doi: S0925492702000021 [pii]

Fitzgerald PB, Brown TL, Daskalakis ZJ, Kulkarni J (2002c) A transcranial magnetic stimulation study of the effects of olanzapine and risperidone on motor cortical excitability in patients with schizophrenia. Psychopharmacology (Berl) 162(1):74–81. doi: 10.1007/s00213-002-1068-4

Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, de Castella A, Bradshaw JL, Kulkarni J (2004a) Motor cortical excitability and clinical response to rTMS in depression. J Affect Disord 82(1):71–76. doi: S0165032703002684 [pii] 10.1016/j.jad.2003.09.014

Fitzgerald PB, Brown TL, Marston NA, Oxley T, De Castella A, Daskalakis ZJ, Kulkarni J (2004b) Reduced plastic brain responses in schizophrenia: a transcranial magnetic stimulation study. Schizophr Res 71(1):17–26. doi: 10.1016/j.schres.2004.01.018 S0920996404000453 [pii]

Fitzgerald PB, Brown TL, Marston NA, Oxley TJ, de Castella A, Daskalakis ZJ, Kulkarni J (2003) A transcranial magnetic stimulation study of abnormal cortical inhibition in schizophrenia. Psychiatry Res 118(3):197–207. doi: S0165178103000945 [pii]

Fitzgerald PB, Daskalakis ZJ, Hoy K, Farzan F, Upton DJ, Cooper NR, Maller JJ (2008) Cortical inhibition in motor and non-motor regions: a combined TMS-EEG study. Clin EEG Neurosci 39(3):112–117

Fitzgerald PB, Williams S, Daskalakis ZJ (2009) A transcranial magnetic stimulation study of the effects of cannabis use on motor cortical inhibition and excitability. Neuropsychopharmacology 34(11):2368–2375. doi: npp200971 [pii] 10.1038/npp.2009.71

Frantseva MV, Fitzgerald PB, Chen R, Moller B, Daigle M, Daskalakis ZJ (2008) Evidence for impaired long-term potentiation in schizophrenia and its relationship to motor skill learning. Cereb Cortex 18(5):990–996. doi: bhm151 [pii] 10.1093/cercor/bhm151

Friston KJ (1998) The disconnection hypothesis. Schizophr Res 30(2):115–125. doi: S0920-9964(97)00140-0 [pii]

Goodwin RD, Marusic A, Hoven CW (2003) Suicide attempts in the United States: the role of physical illness. Soc Sci Med 56(8):1783–1788. doi: S0277953602001740 [pii]

Greenberg BD, Ziemann U, Cora-Locatelli G, Harmon A, Murphy DL, Keel JC, Wassermann EM (2000) Altered cortical excitability in obsessive-compulsive disorder. Neurology 54(1):142–147

Greenberg BD, Ziemann U, Harmon A, Murphy DL, Wassermann EM (1998) Decreased neuronal inhibition in cerebral cortex in obsessive-compulsive disorder on transcranial magnetic stimulation. Lancet 352(9131):881–882. doi: S0140-6736(05)60009-8 [pii] 10.1016/S0140-6736(05)60009-8

Grunhaus L, Polak D, Amiaz R, Dannon PN (2003) Motor-evoked potential amplitudes elicited by transcranial magnetic stimulation do not differentiate between patients and normal controls. Int J Neuropsychopharmacol 6(4):371–378. doi: 10.1017/S1461145703003705 S1461145703003705 [pii]

Hallett M (2000) Transcranial magnetic stimulation and the human brain. Nature 406(6792):147–150. doi: 10.1038/35018000

Hanajima R, Ugawa Y, Machii K, Mochizuki H, Terao Y, Enomoto H, Furubayashi T, Shiio Y, Uesugi H, Kanazawa I (2001) Interhemispheric facilitation of the hand motor area in humans. J Physiol 531(Pt 3):849–859. doi: PHY_11264 [pii]

Herbsman T, Forster L, Molnar C, Dougherty R, Christie D, Koola J, Ramsey D, Morgan PS, Bohning DE, George MS, Nahas Z (2009) Motor threshold in transcranial magnetic stimulation: the impact of white matter fiber orientation and skull-to-cortex distance. Hum Brain Mapp 30(7):2044–2055. doi: 10.1002/hbm.20649

Hoppner J, Kunesch E, Grossmann A, Tolzin CJ, Schulz M, Schlafke D, Ernst K (2001) Dysfunction of transcallosally mediated motor inhibition and callosal morphology in patients with schizophrenia. Acta Psychiatr Scand 104(3):227–235. doi: acp247 [pii]

Hoy KE, Georgiou-Karistianis N, Laycock R, Fitzgerald PB (2008) A transcranial magnetic stimulation study of transcallosal inhibition and facilitation in schizophrenia. J Clin Neurosci 15(8):863–867. doi: S0967-5868(07)00524-3 [pii] 10.1016/j.jocn.2007.08.009

Jacobs KM, Donoghue JP (1991) Reshaping the cortical motor map by unmasking latent intracortical connections. Science 251(4996):944–947

Javaid N, Kennedy JL, De Luca V (2011) Ethnicity and Age at Onset in Bipolar Spectrum Disorders. CNS Spectr doi: Javaid [pii]

Kaplan HI, Sadock BJ, Grebb JA (1994) Kaplan and Sadock's synopsis of psychiatry : behavioral sciences, clinical psychiatry. Williams & Wilkins, Baltimore

Karno M, Golding JM, Sorenson SB, Burnam MA (1988) The epidemiology of obsessive-compulsive disorder in five US communities. Arch Gen Psychiatry 45(12):1094–1099

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62(6):593–602. doi: 62/6/593 [pii] 10.1001/archpsyc.62.6.593

Koch G, Ribolsi M, Mori F, Sacchetti L, Codeca C, Rubino IA, Siracusano A, Bernardi G, Centonze D (2008) Connectivity between posterior parietal cortex and ipsilateral motor cortex is altered in schizophrenia. Biol Psychiatry 64(9):815–819. doi: S0006-3223(08)00690-2 [pii] 10.1016/j.biopsych.2008.05.026

Krnjevic K (1997) Role of GABA in cerebral cortex. Can J Physiol Pharmacol 75(5):439–451

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501–519

Lefaucheur JP, Lucas B, Andraud F, Hogrel JY, Bellivier F, Del Cul A, Rousseva A, Leboyer M, Paillere-Martinot ML (2008) Inter-hemispheric asymmetry of motor corticospinal excitability in major depression studied by transcranial magnetic stimulation. J Psychiatr Res 42(5):389–398. doi: S0022-3956(07)00056-8 [pii] 10.1016/j.jpsychires.2007.03.001

Levinson AJ, Fitzgerald PB, Favalli G, Blumberger DM, Daigle M, Daskalakis ZJ (2010) Evidence of cortical inhibitory deficits in major depressive disorder. Biol Psychiatry 67(5):458–464. doi: S0006-3223(09)01152-4 [pii] 10.1016/j.biopsych.2009.09.025

Levinson AJ, Young LT, Fitzgerald PB, Daskalakis ZJ (2007) Cortical inhibitory dysfunction in bipolar disorder: a study using transcranial magnetic stimulation. J Clin Psychopharmacol 27(5):493–497. doi: 10.1097/jcp.0b013e31814ce524 00004714-200710000-00014 [pii]

Liu SK, Fitzgerald PB, Daigle M, Chen R, Daskalakis ZJ (2009) The relationship between cortical inhibition, antipsychotic treatment, and the symptoms of schizophrenia. Biol Psychiatry 65(6):503–509. doi: S0006-3223(08)01104-9 [pii] 10.1016/j.biopsych.2008.09.012

Maeda F, Keenan JP, Pascual-Leone A (2000) Interhemispheric asymmetry of motor cortical excitability in major depression as measured by transcranial magnetic stimulation. Br J Psychiatry 177:169–173

Manchia M, Lampus S, Chillotti C, Sardu C, Ardau R, Severino G, Del Zompo M (2008) Age at onset in Sardinian bipolar I patients: evidence for three subgroups. Bipolar Disord 10(3):443–446. doi: BDI572 [pii] 10.1111/j.1399-5618.2007.00572.x

Manganotti P, Bortolomasi M, Zanette G, Pawelzik T, Giacopuzzi M, Fiaschi A (2001) Intravenous clomipramine decreases excitability of human motor cortex. A study with paired magnetic stimulation. J Neurol Sci 184(1):27–32. doi: S0022510X00004950 [pii]

McClintock SM, Freitas C, Oberman L, Lisanby SH, Pascual-Leone A (2011) Transcranial magnetic stimulation: a neuroscientific probe of cortical function in schizophrenia. Biol Psychiatry 70(1):19–27. doi: S0006-3223(11)00217-4 [pii] 10.1016/j.biopsych.2011.02.031

Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET (2008) Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 32(3):525–549. doi: S0149-7634(07)00114-5 [pii] 10.1016/j.neubiorev.2007.09.005

Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, Viana MC, Andrade LH, Hu C, Karam EG, Ladea M, Medina-Mora ME, Ono Y, Posada-Villa J, Sagar R, Wells JE, Zarkov Z (2011) Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 68(3):241–251. doi: 68/3/241 [pii] 10.1001/archgenpsychiatry.2011.12

Minelli A, Bortolomasi M, Scassellati C, Salvoro B, Avesani M, Manganotti P (2010) Effects of intravenous antidepressant drugs on the excitability of human motor cortex: a study with paired magnetic stimulation on depressed patients. Brain Stimul 3(1):15–21. doi: S1935-861X(09)00052-7 [pii] 10.1016/j.brs.2009.04.003

Munchau A, Langosch JM, Gerschlager W, Rothwell JC, Orth M, Trimble MR (2005) Mirtazapine increases cortical excitability in healthy controls and epilepsy patients with major depression. J Neurol Neurosurg Psychiatry 76(4):527–533. doi: 76/4/527 [pii] 10.1136/jnnp.2004.037010

Nakamura H, Kitagawa H, Kawaguchi Y, Tsuji H (1997) Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans. J Physiol 498(Pt 3):817–823

Navarro R, Zarkowski P, Sporn A, Avery D (2009) Hemispheric asymmetry in resting motor threshold in major depression. J ECT 25(1):39–43. doi: 10.1097/YCT.0b013e3181761cf5

Oxley T, Fitzgerald PB, Brown TL, de Castella A, Daskalakis ZJ, Kulkarni J (2004) Repetitive transcranial magnetic stimulation reveals abnormal plastic response to premotor cortex stimulation in schizophrenia. Biol Psychiatry 56(9):628–633. doi: S0006-3223(04)00937-0 [pii] 10.1016/j.biopsych.2004.08.023

Pantelis C, Lambert TJ (2003) Managing patients with "treatment-resistant" schizophrenia. Med J Aust 178 Suppl:S62–S66. doi: pan10585_fm [pii]

Pascual-Leone A, Manoach DS, Birnbaum R, Goff DC (2002) Motor cortical excitability in schizophrenia. Biol Psychiatry 52(1):24–31. doi: S0006322302013173 [pii]

Paulus W, Classen J, Cohen LG, Large CH, Di Lazzaro V, Nitsche M, Pascual-Leone A, Rosenow F, Rothwell JC, Ziemann U (2008) State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimul 1(3):151–163. doi: S1935-861X(08)00038-7 [pii] 10.1016/j.brs.2008.06.002

Puri BK, Davey NJ, Ellaway PH, Lewis SW (1996) An investigation of motor function in schizophrenia using transcranial magnetic stimulation of the motor cortex. Br J Psychiatry 169(6):690–695

Rajji TK, Liu SK, Frantseva MV, Mulsant BH, Thoma J, Chen R, Fitzgerald PB, Daskalakis ZJ (2011) Exploring the effect of inducing long-term potentiation in the human motor cortex on motor learning. Brain Stimul 4(3):137–144. doi: S1935-861X(10)00134-8 [pii] 10.1016/j.brs.2010.09.007

Reid PD, Daniels B, Rybak M, Turnier-Shea Y, Pridmore S (2002) Cortical excitability of psychiatric disorders: reduced post-exercise facilitation in depression compared to schizophrenia and controls. Aust N Z J Psychiatry 36(5):669–673. doi: 1082 [pii]

Richter MA, de Jesus DR, Hoppenbrouwers S, Daigle M, Deluce J, Ravindran LN, Fitzgerald PB, Daskalakis ZJ (2012) Evidence for cortical inhibitory and excitatory dysfunction in obsessive compulsive disorder. Neuropsychopharmacology 37(5):1144-1151. doi:npp2011300 [pii] 10.1038/npp.2011.300

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH et al (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 91(2):79–92

Samii A, Wassermann EM, Ikoma K, Mercuri B, George MS, O'Fallon A, Dale JK, Straus SE, Hallett M (1996a) Decreased postexercise facilitation of motor evoked potentials in patients with chronic fatigue syndrome or depression. Neurology 47(6):1410–1414

Samii A, Wassermann EM, Ikoma K, Mercuri B, Hallett M (1996b) Characterization of postexercise facilitation and depression of motor evoked potentials to transcranial magnetic stimulation. Neurology 46(5):1376–1382

Sanger TD, Garg RR, Chen R (2001) Interactions between two different inhibitory systems in the human motor cortex. J Physiol 530(Pt 2):307–317. doi: PHY_11174 [pii]

Schieber MH, Hibbard LS (1993) How somatotopic is the motor cortex hand area? Science 261(5120):489–492

Shajahan PM, Glabus MF, Gooding PA, Shah PJ, Ebmeier KP (1999a) Reduced cortical excitability in depression. Impaired post-exercise motor facilitation with transcranial magnetic stimulation. Br J Psychiatry 174:449–454

Shajahan PM, Glabus MF, Jenkins JA, Ebmeier KP (1999b) Postexercise motor evoked potentials in depressed patients, recovered depressed patients, and controls. Neurology 53(3):644–646

Siebner HR, Dressnandt J, Auer C, Conrad B (1998) Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. Muscle Nerve 21(9):1209–1212. doi: 10.1002/(SICI)1097-4598(199809)21:9<1209::AID-MUS15>3.0.CO;2-M [pii]

Soubasi E, Chroni E, Gourzis P, Zisis A, Beratis S, Papathanasopoulos P (2010) Cortical motor neurophysiology of patients with schizophrenia: a study using transcranial magnetic stimulation. Psychiatry Res 176(2–3):132–136. doi: S0165-1781(09)00158-9 [pii] 10.1016/j.psychres.2009.04.003

Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J (2000) Induction of plasticity in the human motor cortex by paired associative stimulation. Brain 123(Pt 3):572–584

Stephan KE, Baldeweg T, Friston KJ (2006) Synaptic plasticity and dysconnection in schizophrenia. Biol Psychiatry 59(10):929–939. doi: S0006-3223(05)01269-2 [pii] 10.1016/j.biopsych.2005.10.005

Tergau F, Wanschura V, Canelo M, Wischer S, Wassermann EM, Ziemann U, Paulus W (1999) Complete suppression of voluntary motor drive during the silent period after transcranial magnetic stimulation. Exp Brain Res 124(4):447–454

Valls-Sole J, Pascual-Leone A, Wassermann EM, Hallett M (1992) Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr Clin Neurophysiol 85(6):355–364

van Os J, Kapur S (2009) Schizophrenia. Lancet 374(9690):635–645. doi: S0140-6736(09)60995-8 [pii] 10.1016/S0140-6736(09)60995-8

Voineskos AN, Farzan F, Barr MS, Lobaugh NJ, Mulsant BH, Chen R, Fitzgerald PB, Daskalakis ZJ (2010) The role of the corpus callosum in transcranial magnetic stimulation induced interhemispheric signal propagation. Biol Psychiatry 68(9):825–831. doi: S0006-3223(10)00654-2 [pii] 10.1016/j.biopsych.2010.06.021

Wagner T, Valero-Cabre A, Pascual-Leone A (2007) Noninvasive human brain stimulation. Annu Rev Biomed Eng 9:527–565. doi: 10.1146/annurev.bioeng.9.061206.133100

Werhahn KJ, Kunesch E, Noachtar S, Benecke R, Classen J (1999) Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. J Physiol 517 (Pt 2):591–597. doi: PHY_9281 [pii]

Wobrock T, Hasan A, Malchow B, Wolff-Menzler C, Guse B, Lang N, Schneider-Axmann T, Ecker UK, Falkai P (2010) Increased cortical inhibition deficits in first-episode schizophrenia with comorbid cannabis abuse. Psychopharmacology (Berl) 208(3):353–363. doi: 10.1007/s00213-009-1736-8

Wobrock T, Schneider-Axmann T, Retz W, Rosler M, Kadovic D, Falkai P, Schneider M (2009) Motor circuit abnormalities in first-episode schizophrenia assessed with transcranial magnetic stimulation. Pharmacopsychiatry 42(5):194–201. doi: 10.1055/s-0029-1224137

Wobrock T, Schneider M, Kadovic D, Schneider-Axmann T, Ecker UK, Retz W, Rosler M, Falkai P (2008) Reduced cortical inhibition in first-episode schizophrenia. Schizophr Res 105(1-3):252–261. doi: S0920-9964(08)00277-6 [pii] 10.1016/j.schres.2008.06.001

Zarkowski P, Navarro R, Pavlicova M, George MS, Avery D (2009) The effect of daily prefrontal repetitive transcranial magnetic stimulation over several weeks on resting motor threshold. Brain Stimul 2(3):163–167. doi: 10.1016/j.brs.2009.02.001

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996) Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 40(3):367–378. doi: 10.1002/ana.410400306

Ziemann U, Tergau F, Wischer S, Hildebrandt J, Paulus W (1998) Pharmacological control of facilitatory I-wave interaction in the human motor cortex. A paired transcranial magnetic stimulation study. Electroencephalogr Clin Neurophysiol 109(4):321–330

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