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REVIEW

Mapping causal interregional influences with concurrent TMS–fMRI

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Abstract Transcranial magnetic stimulation (TMS) produces a direct causal effect on brain activity that can now be studied by new approaches that simultaneously combine TMS with neuroimaging methods, such as functional magnetic resonance imaging (fMRI). In this review we highlight recent concurrent TMS–fMRI studies that illustrate how this novel combined technique may provide unique insights into causal interactions among brain regions in humans. We show how fMRI can detect the spatial topography of local and remote TMS effects and how these may vary with psychological factors such as task-state. Concurrent TMS–fMRI may furthermore reveal how the brain adapts to so-called virtual lesions induced by TMS, and the distributed activity changes that may underlie the behavioural consequences often observed during cortical stimulation with TMS. We argue that combining TMS with neuroimaging techniques allows a further step in understanding the physiological underpinnings of *TMS, as well as the neural correlated of TMS-evoked consequences on perception and behaviour*. This can provide powerful new insights about causal interactions among brain regions in both health and disease that may ultimately lead to developing more efficient protocols for *basic research* and therapeutic TMS applications.

Keywords Effective connectivity · Dorsal premotor cortex · Top-down control · Virtual lesion · State-dependence · Neuroimaging

Abbreviations

BOLD	Blood-oxygenation-level-dependent
DCM	Dynamic causal modelling
EEG	Electroencephalography
EPI	Echo-planar imaging
FEF	Frontal eye fields
fMRI	Functional magnetic resonance imaging
M1	Primary motor cortex
NIRS	Near-infrared spectroscopy
PET	Positron emission tomography
PMd	Dorsal premotor cortex
IPS	Intraparietal sulcus
TES	Transcranial electrical stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
SoM	Sense of movement

Introduction

Over the last two decades, transcranial magnetic stimulation (TMS) has become a widely successful research

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technique for probing and manipulating brain activity non-invasively in humans (Chambers and Mattingley 2005; Curra et al. 2002; George et al. 2003; Hallett 2007; Pascual-Leone et al. 2000; Sack 2006; Siebner and Rothwell 2003). When neural populations targeted by TMS (Di Lazzaro et al. 1998; Di Lazzaro et al. 2004; Rothwell 1997) are involved in processing an ongoing task, then this stimulation can transiently interfere with the pattern of activity that would usually underlie processing in that task. The resulting behavioural changes (in reaction times or accuracy) can be seen as evidence for a causal role of the stimulated area in the cognitive operations under investigation (Pascual-Leone et al. 1999; Walsh and Cowey 2000). In healthy volunteers, this 'neurodisruption' approach has therefore become a popular method for studying the causal relationship between particular cortical areas and behaviour.

The recent successes of TMS for studies in the cognitive and clinical neurosciences contrast with a still incomplete understanding of how TMS affects neural processing at the site of stimulation, and potentially in interconnected brain regions. For example, TMS may not only directly activate local neurons and intracortical connections but also some interregional connections. Alternatively, TMS might cause adaptive and compensatory changes in distant brain regions as a response to interfering with activity at the stimulation site. Using standard TMS applications on their own typically cannot reveal such remote effects, with inferences usually restricted to the targeted site of stimulation. However, new information about TMS-evoked *inter*-regional influences can now be obtained by combining TMS with neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), or electroencephalography (EEG).

Here we review how the novel combination of TMS with one of these neuroimaging techniques, fMRI, can provide a powerful tool to investigate the neural underpinnings of TMS, as well as a method to assess the impact of one brain region upon interconnected areas, with reasonable spatial precision, non-invasively in healthy human subjects and patients. First, we briefly review the basic principles, and merits of TMS and fMRI in their own right. We then go on to consider why combining these two techniques can provide important new information that is more than the sum of both methods used in isolation. In the remainder of this article, we then provide examples about the different approaches in which concurrent TMS–fMRI can be employed, and the types of question that can be addressed in this way. We illustrate how concurrent TMS–fMRI can be used in a 'perturb-and-measure' approach (Paus 2005), to map not only local but also distributed brain activity changes, as caused by direct stimulation of a cortical region. These examples focus largely on TMS applied to the motor system, which for historical reasons has been targeted the most in this approach. We then go on to illustrate how TMS–fMRI may reveal top–down influences between brain areas, focussing on recent examples from the human visual-attentional network. We further illustrate how one can study the state-dependence of causal interactions among remote and interconnected brain regions, using recent examples in the motor, somatosensory, and visual domain. We argue that combined TMS-neuroimaging approaches such as TMS–fMRI can provide detailed and testable hypotheses about the behavioural significance of remote TMS-evoked activity changes. Moreover, we consider the interesting prospect of using TMS–fMRI for studying activity changes in task-related cortical networks in response to the transient disruption of a task-relevant cortical region, so-called 'virtual lesions' (Pascual-Leone et al. 1999, 2000). Finally, we discuss how concurrent TMS–fMRI can inform and guide possible clinical applications of TMS. Additional technical details regarding the combination of TMS and fMRI are discussed in more detail in an online appendix (see online Supplementary Information).

Transcranial magnetic stimulation

A single TMS stimulus is produced by discharging a short (~1 ms) but strong (several kA) electrical current through a coil of wire placed over a cortical region of interest. The electric pulse induces a time-varying magnetic field perpendicular to the stimulation coil, which passes through the scalp without attenuation. This magnetic pulse in turn induces an electric current in the underlying brain tissue, which can elicit action potentials in neuronal populations nearby (Epstein 2008; Roth et al. 1991a, b; Rothwell 1997; Wagner et al. 2007). The induced magnetic field (which is responsible for inducing current in the brain) is inversely proportional to the square of the distance between coil and cortex (Ilmoniemi et al. 1999; Wagner et al. 2007). Direct effects of stimulation are therefore more or less restricted to the cortex close to the outer convexity of the brain. The concomitant stimulation of the scalp is painless, and in most cases TMS can therefore be applied without problems even in patients.

In primary motor cortex (M1), the effects of stimulation can be readily assessed because, at sufficiently high intensities, TMS causes activity in corticospinal pyramidal tract neurons. This leads to motor-evoked muscle potentials contralateral to the stimulation site that can be recorded using electromyography. At low intensities, TMS is thought to predominantly activate intracortical circuits which then synaptically excite corticospinal output (I-waves) (Rothwell 1999). In this case, activation of cortical output should be entirely orthodromic. However, at high intensities, TMS can directly stimulate input and output axons of the cortex

alike and may also activate inputs to an area antidromically. The effects of single TMS pulses are short-lived. When applied over M1, TMS can produce a short period of repetitive discharge in the cortex that in turn makes the corticospinal neurones discharge at frequencies up to 600 Hz for 10 ms or so. This activity is terminated by a series of (~100–200 ms) inhibitory post-synaptic potential that not only suppresses activity produced by the initial TMS pulse, but also ongoing activity in cortical neurones that preceded the pulse. Taking such information together, a detailed overview is now available for the basic electrophysiology and neuropharmacological basis of different TMS protocols applied to M1 (Chen 2004; Di Lazzaro et al. 2004; Hallett 2007; Lee et al. 2006; Reis et al. 2008; Siebner and Rothwell 2003; Ziemann 2004a; Ziemann et al. 2006; Ziemann and Rothwell 2000). As discussed below, in addition to activating corticospinal outputs, TMS can also activate (often at a different threshold) outputs to other structures via callosal, cortico-cortical, corticostriatal and corticopontine projections (Bestmann et al. 2003; Bestmann et al. 2004; Denslow et al. 2005; Massimini et al. 2005; Paus et al. 1998; Siebner et al. 2001; Strafella et al. 2001, 2003; Taylor et al. 2007b). Understanding such remote effects of TMS is an important challenge when attempting to study causal brain–behaviour relationships with TMS.

Functional magnetic resonance imaging in humans

Functional MRI has been extensively used to study the functional neuroanatomy of cognitive processes in the human brain. fMRI measures the local magnetic field inhomogeneities induced by endogenous haemoglobin in red blood cells. The so-called blood-oxygenation-level-dependent (BOLD) signal capitalises on the coupling between cerebral blood flow, neuronal activity and energy utilisation, to allow a non-invasive assay of local activity changes throughout the human brain (Matthews and Jezzard 2004). Research over the past 10 years has established a firm connection between the BOLD signal and neural activity, although the precise relationship between neural and hemodynamic activity remains under intense investigation (Attwell and Iadecola 2002; Attwell and Laughlin 2001; Logothetis and Pfeuffer 2004; Logothetis and Wandell 2004).

Functional MRI provides repeatable functional 'maps' of activity related to sensory, motor or cognitive processing. One needs to appreciate, however, that these maps should be interpreted with caution with respect to the specific contributions of inhibitory and excitatory neural activity. For example, inhibitory processes can lead to both BOLD signal increases and decreases (Attwell and Iadecola 2002; Shmuel et al. 2006; Stefanovic et al. 2004). Moreover, microstimulation experiments with invasive electrodes in animal studies have established that BOLD signal changes can in principle occur even in the absence of neuronal spiking output (Tehovnik et al. 2006; Tolias et al. 2005). Close parallels between the electrophysiologically well-characterised inhibitory and excitatory effects of TMS, and increases or decreases in BOLD signal during TMS application, should therefore be made only with considerable caution and appropriate caveats. For most applications in humans, fMRI measures BOLD signal changes with a spatial resolution of a few millimetres, and therefore reflects activity on a mesoscopic scale that will inevitably comprise large populations of both inhibitory and excitatory neurons. The temporal resolution of fMRI is on the order of seconds because changes in blood flow are delayed and more prolonged than the underlying neural responses. However, the hemodynamic lag is highly constant and with appropriate designs to 'de-correlate' events and the corresponding regressors used to test for BOLD signals in fMRI analyses, one can differentiate neural population activity changes to events only a few hundred milliseconds apart (Formisano and Goebel 2003; Josephs and Henson 1999).

Bringing together TMS with concurrent fMRI

Combining TMS with fMRI allows researchers to stimulate one part of the human brain and measure evoked changes in brain activity not only at that site of stimulation, but also across the entire brain, including even subcortical structures (Fig. 1). This "perturb-and-measure" approach (Paus 2005) can in principle characterise the spatial topography of TMS effects on neural activity both locally and for remote yet interconnected brain regions. TMS allows causal inferences to be made about brain function and behaviour, by providing a direct input into a cortical target that transiently modifies neural activity. This can bypass the sensory pathways that provide the conventional alternative source of causal inputs. Combining TMS with concurrent neuroimaging, such as fMRI, can allow measurement of any activity changes throughout the brain that result from this direct application of TMS to one targeted cortical region.

Other combinations of TMS with different neuroimaging techniques provide important alternative approaches for studying interregional interactions with TMS that can further complement the TMS–fMRI combination which we focus on here. Those further approaches include the combination of TMS with EEG (Ilmoniemi and Karhu 2008; Kahkonen et al. 2005; Komssi et al. 2002; Massimini et al. 2005; Nikulin et al. 2003; Paus et al. 2001b; Romei et al. 2007, 2008; Taylor et al. 2007b; Taylor et al. 2007a; Virtanen et al. 1999); or with PET (Fox et al. 1997; Paus et al. 1998, 2001a; Paus 2005; Paus 1999; Siebner et al. 1998, 2000, 2003b, 2008; Speer et al. 2003); or with near-infrared spectroscopy (NIRS) (Hanaoka et al. 2007; Mochizuki

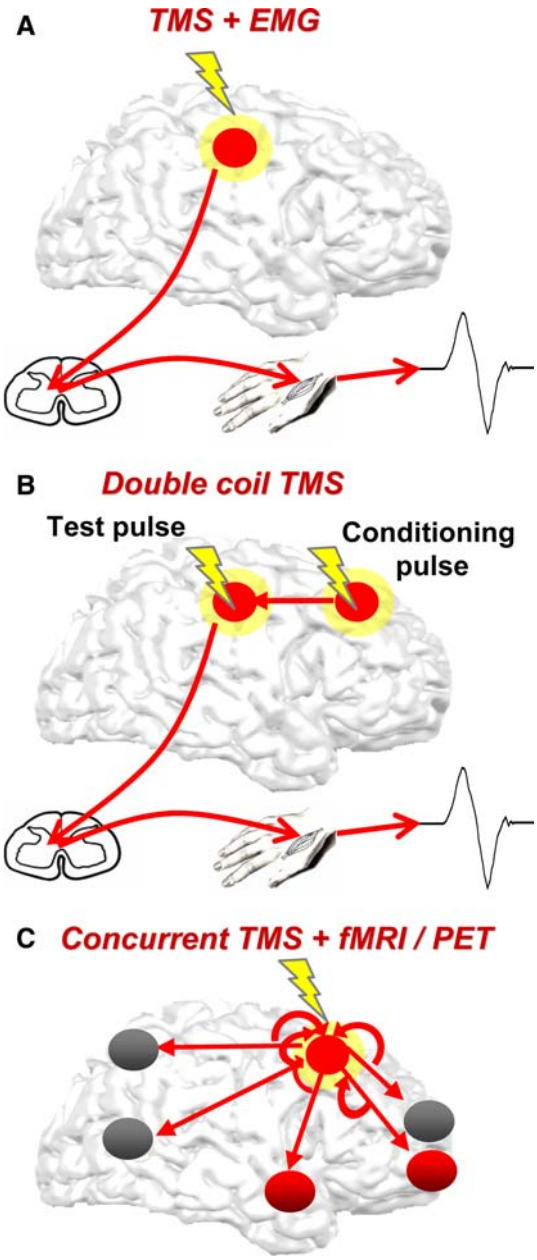

Fig. 1 Using TMS to investigate causal interactions in the human brain. **a** TMS applied to primary motor cortex (M1) elicits contralateral muscle movements that can be recorded with electromyography. This permits insight into corticospinal causal interactions, but is limited to these. **b** TMS double-coil approaches test whether stimulation of a cortical region that is connected to M1 may exert causal influences upon M1, as quantified by recordings of contralateral muscle potentials. Due to the excellent temporal precision of TMS, this approach enables the investigation of the temporal organisation of such causal interactions. **c** Combined TMS and neuroimaging approaches can assess the impact of stimulation across multiple cortical (*grey ellipsoids*) and subcortical (*red ellipsoids*) regions, for many potential sites other than M1

et al. 2006, 2007; Oliviero et al. 1999). Overall, such studies have employed TMS in two very different ways that need to be distinguished. On the one hand, repetitive TMS (rTMS) can be used in an 'off-line' approach to induce lasting plasticity-like changes in cortex (Classen and Stefan 2008; Siebner and Rothwell 2003; Ziemann 2004b). These changes can depend on the prior history of activation before rTMS is applied (Huang et al. 2008; Touge et al. 2001). Combined 'off-line' TMS with neuroimaging seeks to study prolonged changes induced by the preceding rTMS (Chouinard et al. 2003; Classen and Stefan 2008; Hubl et al. 2008; Lee et al. 2003; O'Shea et al. 2007a; Paus 1999; Pleger et al. 2006a, b; Siebner et al. 2003a, b; Tegenthoff et al. 2005). Such approaches do not necessarily require the concurrent and simultaneous combination of TMS with neural measures, because the effects of rTMS can outlast the period of stimulation. In contrast, the immediate 'on-line' effects of TMS can be studied instead when using single pulse TMS or short burst TMS protocols. These 'on-line' TMS applications are ideally suited to event-related trial-by-trial investigations. One can thereby study the effects of each TMS pulse or short pulse-series without considering longer lasting effects. In the remainder of this review paper we will focus specifically upon 'on-line' use of concurrent TMS–fMRI, and hence on questions for which this online combination of methods seems particularly suitable.

Combining TMS with fMRI concurrently poses a number of challenging methodological problems. Bohning and colleagues were the first to demonstrate the technical feasibility of concurrent TMS–fMRI (Bohning et al. 1998, 1999; Roberts et al. 1997), and subsequent developments have further improved the quality of MR images that can be obtained during scanning (for review, see Bestmann et al. 2008a). A more detailed overview of the methodological considerations that must be considered for concurrent TMS–fMRI applications can be found in the online Supplemental Material that accompanies this article.

Combining TMS and neuroimaging in animals

Recent combinations of TMS with direct electrophysiological recordings (Allen et al. 2007; Aydin-Abidin et al. 2006; de Labra et al. 2007; Moliadze et al. 2003, 2005), metabolic (Valero-Cabre et al. 2005), or with optical imaging techniques (Allen et al. 2007) in animals have provided some unique insight into TMS effects, not just for M1 but for other neural structures also including primary visual cortex (V1). These studies show that a single TMS pulse can elicit a series of excitatory postsynaptic potentials (EPSPs) in a large population of neurons, followed by a series of generalized inhibitory postsynaptic potentials (IPSPs) lasting up to 200 ms (Moliadze et al. 2003). Other studies have investigated in detail the neural underpinnings of paired-pulse (Moliadze et al. 2005) and rTMS protocols on neural activity as assessed directly (Aydin-Abidin et al. 2006; de Labra et al. 2007). In a recent study by Allen et al. (2007), the

effects of TMS on cat visual cortex were assessed using a combination of single unit, local field potential (LFP), tissue oxygenation and hemodynamic recordings. The authors demonstrated that the effects of rTMS to visual cortex are more pronounced when using longer TMS trains and higher stimulation frequencies. Furthermore, these effects can depend on the state of the stimulated area, with more marked effects of TMS on responses evoked by strong external input (here by visual stimulation) than on ongoing resting activity. This suggests that under some circumstances TMS may specifically disrupt the excitability of a cortical region to inputs and thereby reduce net evoked activity. These TMS-evoked neural changes were closely coupled with hemodynamic signal changes over a range of stimulation parameters (Allen et al. 2007). Moreover, those authors could demonstrate that TMS leads to an initial increase and subsequent longer lasting decrease in tissue oxygenation and haemoglobin concentration. These findings are of particular relevance for combined TMS and neuroimaging studies in humans, for several reasons. They demonstrate that TMS-evoked neural activity and the resulting cerebral hemodynamics (which underlie the signal measured with fMRI) are indeed tightly coupled; that these effects are dose-dependent, i.e. depend on stimulation frequency, intensity, and duration; and that they depend on the current activation state of stimulated cortex (Allen et al. 2007).

These findings can furthermore be compared to studies using electrical microstimulation combined with simultaneous fMRI in animals (Ekstrom et al. 2008; Moeller et al. 2008; Tolias et al. 2005). One important observation is that microstimulation is capable of activating cells in remote but connected brain regions, sometimes more than one synapse away. It seems feasible to assume that similar effects may arise during TMS, although experiments in humans necessarily lack the fine-grained anatomical and neurophysiological precision with which such stimulation can be performed in such more invasive animal work. It is important to emphasize that analogies between TMS-evoked inhibition, excitation, or neuromodulation, as studied with direct invasive methods, and the less direct measure of BOLD signal increases or decreases during fMRI, require some caution, given the nature of the BOLD response. Nevertheless, TMS and microstimulation studies in animals already give some grounds for confidence that combining TMS and fMRI in humans might shed useful light on the local and remote consequences of stimulating a targeted cortical region with TMS.

Using concurrent fMRI to assess local and inter-regional activity changes evoked by TMS at rest

The initial studies to use concurrent TMS–fMRI examined effects of stimulating M1 (Bohning et al. 1998, 1999, 2000a, b), since results for this TMS site could be compared directly with the information available from the extensive neurophysiological studies using traditional EMG methods. In addition, localisation of the target region is straightforward and can be validated by evoking contralateral hand muscle movements. One important initial finding was that even relatively short applications of online TMS can evoke activity in areas remote from the stimulation site (Baudewig et al. 2001b; Bohning et al. 1999, 2000a, b), including supplementary motor area (SMA) and premotor cortices. Another important observation was that the impact of stimulation was dose-dependent (Bohning et al. 1999, 2003), as stronger stimulation intensities evoked larger activity changes in those regions.

A potential difficulty when interpreting activity changes during stimulation of M1 at suprathreshold intensities is the likely contribution of afferent feedback from contralateral muscle responses (Fig. 2). Because primary somatosensory and M1 are intimately interconnected, the contributions from efferent descending corticospinal signals, afferent feedback arising consequent to an induced twitch, and the processing of this feedback may be difficult to disentangle with fMRI during TMS-evoked muscle movements. Indeed, active and passive finger movements elicit similar activity changes in M1 and fronto-parietal regions (Balslev et al. 2006; Radovanovic et al. 2002; Reddy et al. 2001). Several studies reported that TMS administered at intensities below the threshold for evoking contralateral movements does not consistently provoke significant BOLD signal changes in M1 (Baudewig et al. 2001b; Bestmann et al. 2003, 2004, 2005; Bohning et al. 2000b; Denslow et al. 2005; Li et al. 2004a), despite the known impact of TMS below motor threshold on neuronal activity at the site of stimulation (Di Lazzaro et al. 2004; Kujirai et al. 1993). Similarly, when short bursts of TMS applied to dorsal premotor cortex (PMd) did not evoke any peripheral muscle response, this only led to BOLD activity increases at the stimulation site for stimulation intensities above resting motor threshold for M1 stimulation (Bestmann et al. 2005). The apparent difference in the threshold for electrophysiological and BOLD effects may reflect an intrinsic difference in the sensitivity of the two measures. However, further technological improvements are likely to enhance the sensitivity of combined TMS–fMRI and so may reduce this apparent difference.

In contrast, activity changes in remote but interconnected regions have consistently been observed with various TMS protocols, even in the absence of significant changes in activity at the stimulation site, using either fMRI (Bestmann et al. 2003, 2004; Bohning et al. 1999; Denslow et al. 2005) or PET (Chouinard et al. 2003; Kimbrell et al. 2002; Rounis et al. 2006; Speer et al. 2003). For example, TMS to M1 or PMd can evoke significant activity changes

in remote regions of the motor system (Bestmann et al. 2003, 2004, 2005); see Fig. 2. These remote activity changes cannot be attributed to re-afferent feedback from activation of peripheral muscles because the remote activity changes were observed even at M1 stimulation intensities below threshold for activating corticospinal pathways (Fig. 2), and because TMS over non-primary motor areas does not normally cause peripheral muscle activation (Bestmann et al. 2005, 2008b).

Recent double-coil TMS studies that investigated cortical influences on M1 further support the finding that even single TMS pulses can influence activity in remote brain regions. The double-coil TMS approach applies a conditioning pulse to one brain region, while a subsequent test pulse is delivered to M1, or primary visual cortex (Fig. 1b). One can thereby study the fine-grained temporal dynamics of causal interactions between a targeted (conditioned) cortical region and M1 or V1. For example, single pulses of subthreshold TMS applied to premotor sites can have significant impact on the excitability of both ipsi- and contralateral M1 (Civardi et al. 2001; Koch et al. 2006, 2007; Munchau et al. 2002; O'Shea et al. 2007b) and these can be modulated during movement planning versus rest (Koch et al. 2006, 2007; O'Shea et al. 2007b). One advantage of

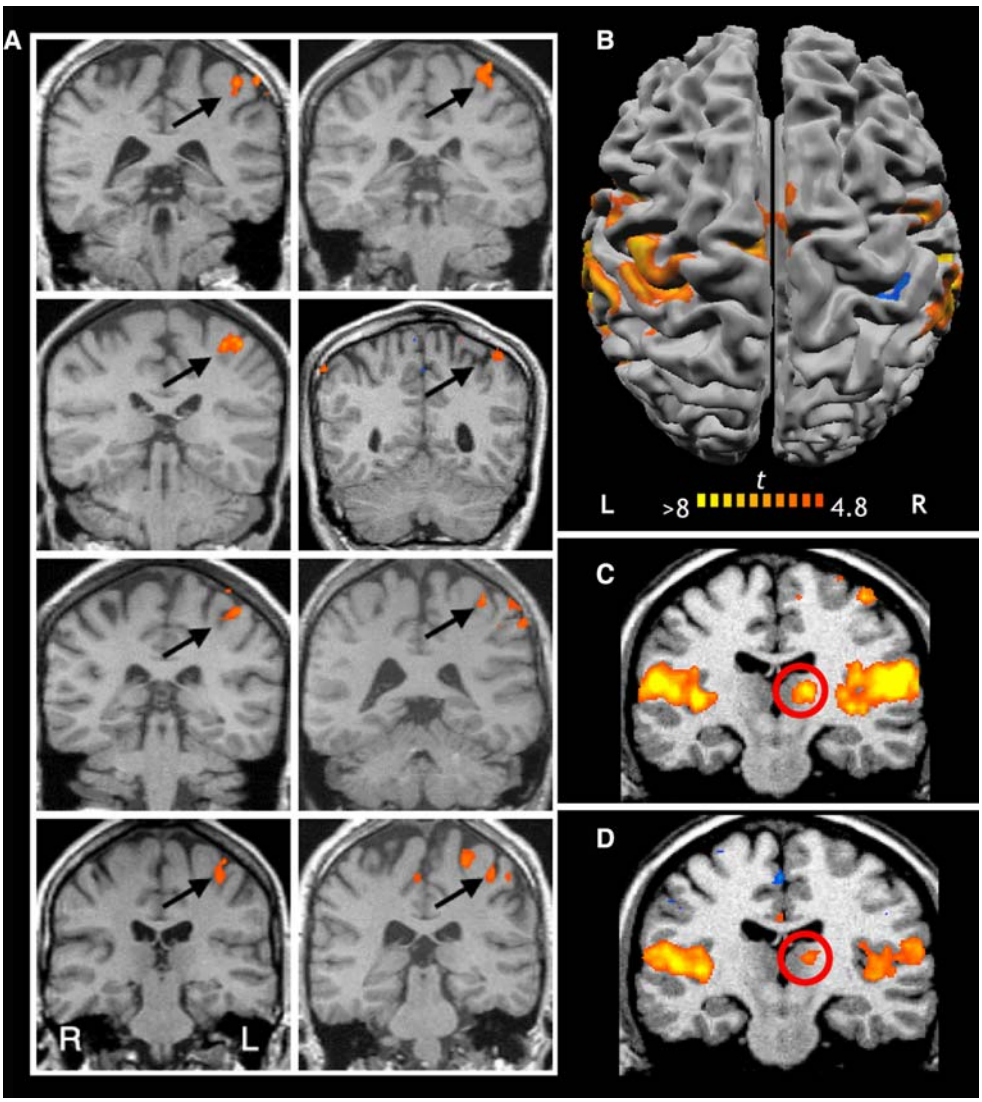

Fig. 2 **a** Individual activation maps (coronal sections) from eight subjects obtained for suprathreshold rTMS applied at 110% of resting motor threshold over the left M1 hand region. At these intensities, activity consistently increases in M1 in individual subjects. **b**, **c** Suprathreshold M1 stimulation at rest additionally evokes widespread activity changes in secondary motor regions and the thalamus, but also auditory and somatosensory cortex due to non-specific aspects of TMS discharge. **d** Even at subthreshold intensities, remote activity changes, including the ventro-lateral thalamus and putamen, can be observed. Subthreshold stimulation does not elicit electromyographic responses in contralateral muscles, ruling out contributions of afferent feedback from contralateral muscle activation (adapted from Bestmann et al. 2003, 2004). *L* left hemisphere, *R* right

the double-coil TMS approach is the fine-grained temporal resolution that can be obtained. The main limitation is that the method is restricted to examining influences upon M1 or primary visual cortex (Pascual-Leone and Walsh 2001) in particular, whereas in principle concurrent TMS–fMRI allows remote influences to be assessed across the entire brain.

Using concurrent TMS–fMRI to map causal top–down influences: recent examples from the human visual system

A recent series of studies has moved well beyond the motor system per se, using concurrent TMS–fMRI as a novel approach for studying whether specific parietal and frontal regions can exert top–down influences upon processing in visual cortex. It has long been argued on indirect grounds that frontal and parietal cortex may have specific roles in top–down control of visual cortex (Corbetta and Shulman 2002; Desimone and Duncan 1995; Driver 2001). Recent microstimulation studies in non-human primates have shown that the macaque frontal eye fields (FEF) can modulate activity in posterior visual cortex (Ekstrom et al. 2008; Moore and Armstrong 2003), providing direct evidence for a role of the FEF in top–down visual control. While human neuroimaging studies have appeared broadly consistent with fronto-parietal regions exerting top–down control on visual cortex (Corbetta and Shulman 2002; Martinez et al. 1999; Schluppeck et al. 2006; Tootell et al. 1998), they typically cannot reveal a truly causal influence from frontal or parietal cortex upon visual cortex. But by using fMRI in combination with TMS can reveal possible remote top–down influences at the neural population level, complementing invasive microstimulation studies in non-human primates (Armstrong et al. 2006; Moore and Armstrong 2003; Schafer and Moore 2007).

In a pioneering TMS-PET study, Paus et al. (1997) provided the first evidence in humans that TMS to frontal cortex can have remote physiological effects in the human brain. TMS applied to the FEF evoked changes in PET activity for posterior brain regions, including the parieto-occipital sulcus. In three recent studies, Ruff et al. (2006, 2008a, b) used concurrent TMS–fMRI for studying causal interactions in the human visual system, permitting a detailed analysis of the topographic pattern of TMS-evoked activity changes in retinotopic visual areas, including V1–V4 as well as V5/MT+. Short bursts of TMS were applied at parametrically varied intensities to the frontal or parietal eye fields, or to a vertex control site. TMS to the right FEF led to a characteristic pattern of BOLD signal changes in remote, retinotopic visual areas V1–V4 in posterior occipital cortex, with clear intensity dependence for these effects. Critically, the effects had a very specific topographic organisation. Increased TMS intensities over right FEF led to BOLD signal decreases for more foveal visual field representations in V1–V4, but opposite effects (BOLD increases) were found for more peripheral-visual-field representations in retinotopic visual cortex (Fig. 3). These TMS-intensity-dependent effects were not observed during vertex stimulation. Another important observation was that these BOLD response changes were unaffected by the level of background activity in visual cortex, as manipulated by the presence or absence of visual input during TMS. In general accord with microstimulation experiments in non-human primates (Moore and Armstrong 2003), concurrent TMS–fMRI showed that stimulation of the human FEF can affect processing in visual cortex, thereby demonstrating 'top–down' influences on visual cortex. In a subsequent study, stimulation of another cortical region proposed to be involved in top–down visual control—the parietal eye fields (PEF) in the intraparietal sulcus (IPS)—elicited influences on activity in early visual cortex that were significantly different from the FEF-TMS effects in direct comparison (Ruff et al. 2008a). The same TMS protocol, but now applied to right parietal cortex instead, led to activity increases in early visual cortex only during the absence of visual stimulation; but also had an impact on activity in the human motion complex (V5/MT+) only when moving visual input was simultaneously presented. In contrast, no such changes were observed for left parietal TMS (Ruff et al. 2008b).

These studies therefore show how TMS–fMRI can be usefully employed to dissect specific functional contributions of different cortical regions of a cortical network, by virtue of their impact and influence on distant parts of the network when stimulated with TMS. Converging evidence comes from a recent study by Taylor et al. (2007b) who used combined TMS-EEG to study the temporal organisation of top–down influences between the FEF and visual cortex. They reported that stimulation of the right FEF influenced visual ERPs, particularly when attention was directed to the contralateral visual hemifield. Taken together, these combined TMS and neuroimaging (fMRI/EEG) studies provide exciting new insights into the spatial and temporal organisation of causal top–down influences in the human visual system.

Mapping causal interactions and their dependence on current state

Detailed studies of the motor system have revealed that the impact of a TMS pulse depends on the excitability of connections (and/or the current level of activity) at the time the TMS pulse is applied. The more excitable a given connection at the time of stimulation, the more likely it is to be

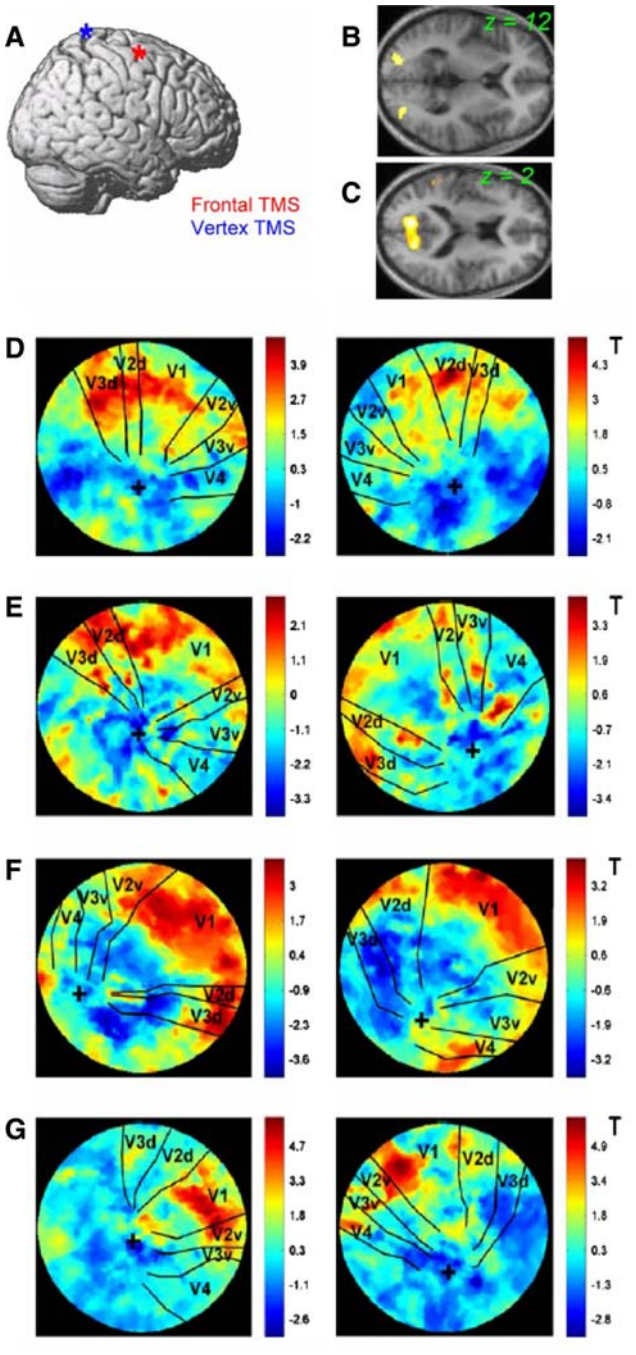

Fig. 3 Top–down influences of TMS to frontal eye fields (*FEF*) upon visual cortex. **a** Stimulation location for frontal TMS, and a vertex control site. A bilateral effect of right FEF-TMS upon visual cortex was found, with BOLD signal increases for peripheral-visual-field representations (**b**), and BOLD signal decreases for central-visual-field representations (**c**). Flatmaps of retinotopic visual areas in four subjects (**d**–**g**) showing BOLD signal increases (*red*) and BOLD signal decreases (*blue*) due to stronger FEF-TMS. The representation of the fovea is indicated approximately by a *cross*. Borders of all mapped visual areas are indicated by *black lines*. Note that for every participant and hemisphere, *hot colours* appear at representations of more peripheral locations in the flatmap of each visual area, whereas the *cold colours* appear closer to the foveal confluence. Left hemisphere is shown on the *left*. Adapted from Ruff et al. (2006)

affected by TMS. For example, applying TMS during voluntary contraction versus rest affects the size and number of descending volleys evoked by TMS of motor cortex (Fujiwara and Rothwell 2004; Mazzocchio et al. 1994; Ridding et al. 1995); the balance between inhibitory and excitatory intracortical systems (Ortu et al. 2008); the amount of inferred interhemispheric inhibition from one motor cortex upon the other (Ferbert et al. 1992); and the coupling between frontal premotor areas and motor cortex (Strens et al. 2002). In visual cortex, recent behavioural studies relying on phosphenes that can be perceived when stimulating visual cortex at an appropriate intensity have demonstrated the state-dependence of TMS-induced effects for vision. A striking example is the change in TMS-evoked phosphenes during migraine (Aurora et al. 1998). Other studies have confirmed the state-dependence of TMS, using spatial attention (Bestmann et al. 2007) or neural adaptation paradigms (Silvanto et al. 2007). Recent work combining TMS and EEG provides further evidence for the state-dependence of TMS effects, showing that the propagation of TMS-evoked activity can depend on the degree of wakefulness at the time of stimulation (Massimini et al. 2005). Using double-coil paired-pulse TMS approaches, state-dependent interactions reflecting action preparation have recently been demonstrated between premotor (Koch et al. 2006; O'Shea et al. 2007b) or parietal cortex (Koch et al. 2007) with M1.

In a recent example in the motor system (Bestmann et al. 2008b), we applied short bursts of TMS (360 ms, 11 Hz) to left PMd during fMRI while subjects engaged in a simple motor task (brief isometric hand grips of the left hand) or maintained rest. Left PMd was studied since it is considered dominant for the selection and preparation of actions (Astafiev et al. 2003; Davare et al. 2006; Rushworth et al. 2003; Schluter et al. 2001). Since the TMS intensity we used was relatively low, there was no disruption of grip behaviour. The TMS pulse was used simply to probe connectivity during the task, via any impact on activity in remote interconnected regions, and any state-dependence for this that would imply changes in 'effective connectivity'.

TMS to left PMd affected activity not only at that site, but also in contralateral right PMd and M1. Moreover, it did so in a different manner, depending on whether subjects were at rest or performing an active left-hand grip (Fig. 4). When participants engaged in a left-hand grip, concurrent high (vs. low) TMS over left PMd increased activity in contralateral right PMd and also right M1. However, during rest, the same stimulation decreased activity in these regions instead. An additional analysis of inter-regional coupling furthermore suggested that coupling between the targeted left PMd and right PMd/M1 was stronger when high intensity TMS was applied during the active left-hand

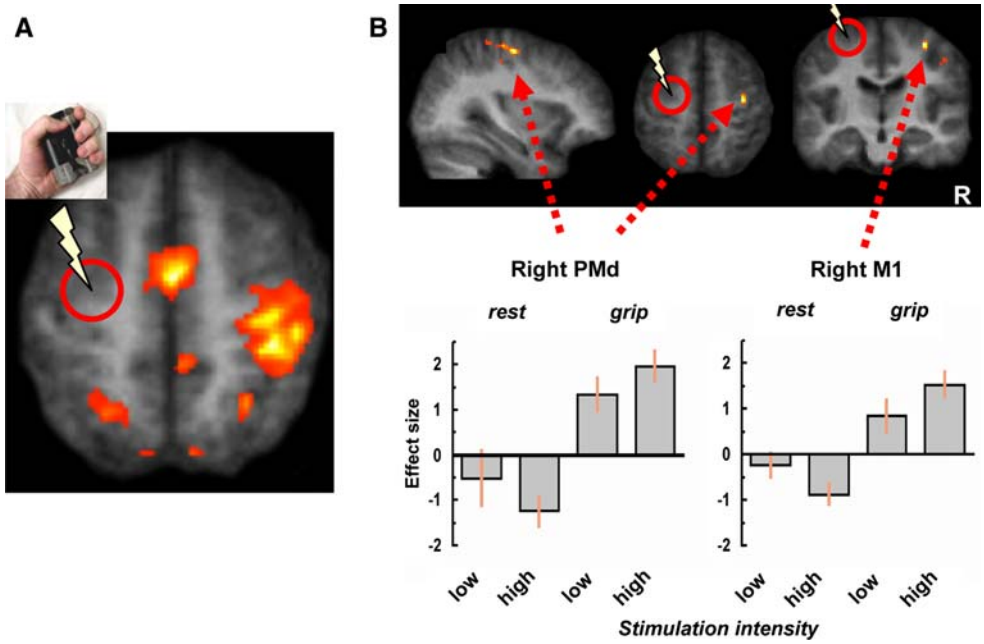

Fig. 4 State-dependent interregional interactions evoked by TMS. **a** During an active left-hand grip task that activated a predominantly right-hemispheric motor network, including M1 and PMd, short TMS bursts were applied to left PMd on every trial. **b** Statistical parametric map of the interaction between TMS intensity and current motor state. The respective parameter estimates of this effect show that TMS above motor threshold (*high*) to left PMd at rest leads to a relative activity decrease in contralateral PMd and M1, as compared with a low intensity control TMS condition (*low*), but to an activity increase when applied during grip (adapted from Bestmann et al. 2008b)

grip task, compared to rest. Thus we can conclude that performance of the active grip task modified interhemispheric interplay between left PMd and contralateral cortical motor regions. Moreover, such influences appeared to be specific to regions currently engaged in a motor task (hand grip), rather than being widely distributed across all putatively interconnected target sites. In keeping with double-coil TMS paired-pulse studies of PMd–M1 interactions (Koch et al. 2007; O'Shea et al. 2007b), these findings suggests that TMS may preferentially activate pathways which at the time of stimulation show an increased effective connectivity with the stimulation site, compared to remote brain regions that may currently not show such a change.

The state-dependence of remote TMS effects was also examined in the above-mentioned studies by Ruff et al. (2006, 2008a, b) in the visual system, but using a somewhat complementary logic. TMS was not used to disrupt behavioural performance, but rather as a controlled input to the targeted (frontal or parietal) regions that should then go on to affect processing in interconnected regions of visual cortex. However, instead of varying the endogenous activation state of the frontal (FEF) or parietal (IPS) regions targeted with TMS (as for the grip-task study described above), the authors varied the level of baseline activity in the visual areas of occipital cortex hypothesized to be affected by TMS. This was achieved by means of visual stimuli that were either present or absent concurrently with TMS. FEF-TMS effects on BOLD signal in visual cortex were not affected by the manipulation of visual state, whereas IPS-TMS effects upon visual areas V1–V4 and V5/MT+ differed qualitatively when concurrent visual stimulation were present versus absent. Those studies thus show clearly that effective connectivity of parietal and occipital regions in the human brain may change with different levels of driving external (visual) input, whereas corresponding influences from frontal regions may be less sensitive to such activity-state manipulations, possibly acting in a top–down manner regardless of current visual input.

Causal interplay among brain regions and corresponding impacts on behaviour

Transcranial magnetic stimulation has been successfully used in the cognitive neurosciences for establishing causal brain–behaviour relationships. This approach has often assumed that the behavioural impacts of TMS may solely reflect functional specialization of the targeted region. However, purely behavioural TMS studies may not reveal whether the behavioural perturbations produced result primarily from interference with the site of stimulation, or may additionally involve influences on remote but interconnected brain regions. Three recent studies show how understanding the spatial topography of TMS influences on remote but interconnected brain regions can help to generate new predictions and explanations about TMS effects on behaviour, and identify the regions involved during behavioural perturbation by TMS.

Blankenburg et al. (2008) hypothesised that enhancements of tactile processing for the ipsilateral hand during right parietal TMS (Seyal et al. 1995) may reflect interhemispheric influences of right parietal cortex on processing in left primary somatosensory cortex, S1. Their concurrent TMS–fMRI study (Blankenburg et al. 2008),

confirmed this prediction, showing TMS to right parietal cortex can indeed increase BOLD signal in left SI (when comparing high- vs. low-intensity TMS) during right-wrist somatosensory input. In contrast, a decrease in left S1 due to TMS was observed instead in the absence of somatosensory input. Moreover, this state-dependent remote modulation of SI activity was accompanied by a related pattern of TMS-induced influences in the thalamus. A subsequent psychophysical experiment again confirmed that these specific state-dependent remote TMS-evoked activity changes have behavioural relevance: right parietal TMS enhanced detection of peri-threshold electrical stimulation of the right median nerve, which is initially processed in left S1 (Blankenburg et al. 2008). This demonstrates that TMS–fMRI can directly assess inter-hemispheric interactions and their functional consequences.

The study of Ruff et al. (2006) mentioned earlier demonstrates that new predictions for behavioural effects of TMS can be derived from findings about the spatial topography of remote influences between brain regions, as observed with TMS–fMRI. Those authors reasoned, based on their TMS–fMRI findings, that FEF stimulation should enhance peripheral vision relative to central, based on the specific pattern of BOLD signal changes they had observed in retinotopic visual cortex. This new prediction was subsequently confirmed in a psychophysical experiment testing the consequences of FEF-TMS (compared to the vertex control site) upon contrasts judgements for Gabor patches presented in the central versus peripheral-visual field. These stimuli activate predominantly early visual cortex, and the behavioural finding was that during FEF-TMS participants showed enhanced contrast perception for peripheral relative to central stimuli. This links the observed remote influences of FEF-TMS upon activity in visual cortex with the functional consequences for perception, suggesting that feedback connections from the FEF to visual cortex may underlie modulatory top–down influences on visual cortex function.

An alternative approach is to use TMS transiently to *disrupt behaviour*, and examine how the brain copes with, or adapts to, the disruption/activation at the stimulation site and interconnected remote regions. If there is functional degeneracy in brain organisation (Friston and Price 2003), then one might potentially expect some reorganisation of activity patterns to compensate and maintain performance. In contrast, if 'on-line' TMS succeeds in producing behavioural change, then there must have been a failure of such mechanisms to adapt fully.

Sack et al. (2007) first applied this rationale to study the contributions of left and right parietal cortex to visuospatial processing during visuospatial judgements. While fMRI studies suggest that visuospatial operations engage regions along the intraparietal sulcus bilaterally, a previous behavioural TMS study reported that only parietal TMS over the *right* hemisphere in particular perturbed visuospatial performance (Sack et al. 2002). In fact, more recent work showed that although the brain can compensate for TMS disruption of left parietal cortex the converse is not true (Sack et al. 2002, 2005). The apparent right-hemispheric dominance of parietal cortex for visuospatial functions, as determined with TMS, does not necessarily indicate that the effect of TMS is solely due to a change in processing at that local site of stimulation. It could be due to more widespread perturbation of task-relevant distributed network activity. Sack et al. (2007) used concurrent TMS–fMRI to address this. Participants performed a visuospatial task known to engage intraparietal activity bilaterally. While judging the angle formed by the hands of a visually presented analogue clock, TMS was applied to the right IPS on 50% of trials, during scanning, at a time point during the task that was previously identified as critical for task processing (Sack et al. 2002, 2005). TMS to right IPS during visuospatial processing resulted in concomitant activity decreases not only at the stimulation site, but also in remote medial frontal gyrus of the same hemisphere (Fig. 5). This activity decrease at right IPS site and remote ipsilateral medial frontal gyrus was accompanied by, and highly correlated with, a prolongation of reaction times in the visuospatial task. Crucially, these effects were specific to both the visuospatial task and the stimulated region. TMS did not lead to these changes when applied to left intraparietal cortex instead, nor when given to the same (right) intraparietal region during a colour discrimination task that required identifying the colour of a stimulus, rather than its visuospatial properties. In these latter tasks, TMS decreased activity in the SMA, plus FEF, but the effects were not correlated with behavioural performance. The findings therefore provide evidence that behavioural TMS effects may be mediated by disruption of activity not only at the stimulation site, but also in specific interconnected task-relevant brain regions. This illustrates how concurrent TMS–fMRI can map out brain regions mediating the impact of local TMS on task performance (Sack et al. 2007).

Taken together, these studies suggest that the behavioural consequences of TMS to a targeted area may not always be attributable to a perturbation of the stimulated area only. Behavioural perturbations may instead reflect an impact on more extended functional networks, rather than just at the stimulation site alone. Combined approaches such as the concurrent TMS–fMRI methods considered here can now start to identify these networks, and to address questions regarding their functional response to TMS-evoked neurodisruption.

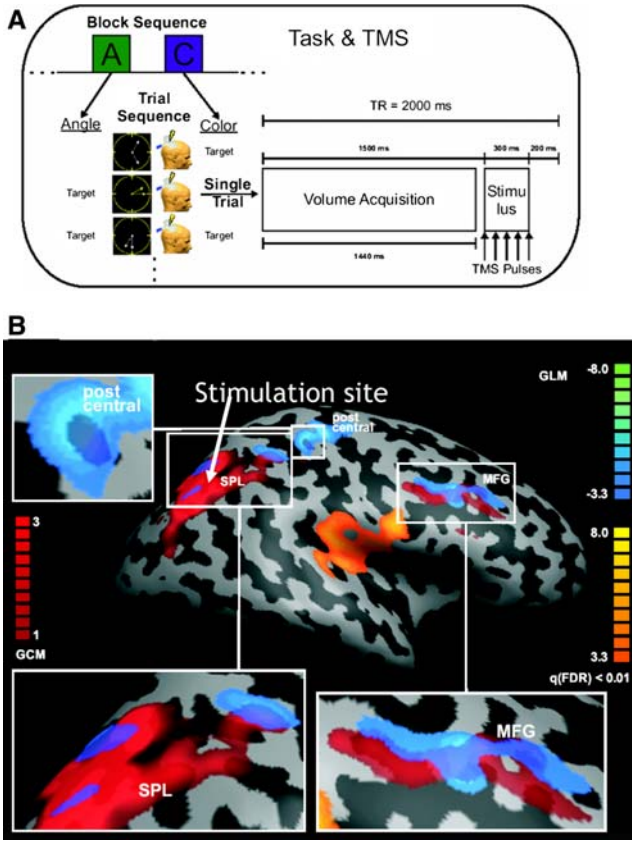

Fig. 5 Visualising virtual lesions reveals an impact on an extended task-related network, not just at the targeted site. **a** Subjects either judged the angle (visuospatial), or the colour (colour discrimination) of the displayed analogue visual clock. During task performance, TMS was applied either to left or right superior parietal lobe (*SPL*). **b** The network of functional connectivity is superimposed on the regions activated for the presence minus absence of right parietal TMS, for the angle task. These results are colour coded in *blue–orange*, *blue* representing areas with a TMS-induced decrease of neural activity during angle task execution. The *red* colour-coded effects represent brain areas showing functional connectivity during the angle task execution. Close-up windows are provided for the three regions-of-interest: right SPL, right postcentral gyrus, and right middle frontal gyrus (*MFG*). This shows that the task-specific TMS-induced activity modulations occur in the same brain areas that are functionally connected during the execution of specifically this visuospatial task. In contrast, this relationship was not observed when the colour task was performed on the identical clock stimuli. Adapted from Sack et al. (2007)

Clinical applications of concurrent TMS–fMRI

One of the most rapidly moving and important applications of TMS is in clinical and therapeutic use, potentially for a wide range of neuro-psychiatric diseases. But this potential widespread use does contrast with the relatively limited understanding about how TMS affects activity in cortical and subcortical networks, and how this may in turn lead to any clinical improvement (Ridding and Rothwell 2007). For example, it is currently unknown whether stimulation protocols that are effective in healthy volunteers are equally effective or suitable for patients. If not, then this may lead to ineffective targeting of the relevant brain structures in clinical groups, either by applying inappropriate stimulation protocols, or by underestimating the exact impact on disease-specific remote (for example, subcortical) brain regions. TMS in combination with neuroimaging can potentially map out the regions altered by TMS in patient populations and thereby inform therapy in a highly concrete way. As considered below, it may even be possible to map out how the local and remote effects of TMS may change in response to neuroactive compounds, in order to promote development of combined therapeutic approaches (e.g. combining specific drugs with specific TMS-interventions) that outperform commonly used TMS protocols.

In one recent example, Nahas et al. (2001) used concurrent TMS–fMRI to investigate the impact of 1 Hz rTMS to left dorsolateral prefrontal cortex (DLPFC) in healthy volunteers, a region commonly targeted in TMS treatment for major depression. This region is often targeted by TMS studies on depression because of its putative strong connections to the subgenual region of the cingulate cortex, an area implicated in depression. Nahas et al. (2001) found that left DLPFC TMS-evoked activity increases near the site of stimulation, as well as in contralateral right DLPFC. These activity increases were 'dose-dependent', increasing with TMS intensity. However, no activity changes in subgenuate brain regions were observed, either indicating that left DLPFC may not be an optimal target to evoke activity in subgenuate and subcortical regions; or that TMS applied to healthy volunteers does not exert comparable effects as in depression.

Applying concurrent TMS–fMRI in depressed patients proved to be an ideal way of answering this question (Li et al. 2004a). When applying 1 Hz TMS for 21 s to left dorsolateral prefrontal cortex, activity increases were found near the stimulation site, as well as in bilateral middle prefrontal cortex, right orbitofrontal cortex, insula, and left hippocampus (Li et al. 2004a), regions commonly involved in mood disorders. The stronger and more widespread activity changes evoked by TMS in these patients, compared to the healthy population studied in Nahas et al. (2001) suggests that the 'reactivity' of some brain networks to TMS may not be the same in health and disease. Other work has used TMS over M1 to identify abnormal synaptic use-dependent plasticity in schizophrenia that related to the aberrant motor behaviour often seen in such patients (Daskalakis et al. 2008). The combined TMS–fMRI approach can provide additional information about the specific circuits exhibiting such abnormal pathophysiological changes, to manifest as altered reactivity of these circuits to TMS.

A different approach is to use combined TMS–fMRI to investigate functional changes, and potential changes in effective connectivity between brain areas, following administration of neuroactive compounds. This approach is motivated by a wealth of studies showing that neuroactive drugs can change cortical excitability and thereby the effectiveness of TMS (Ziemann 2004a). In the first study addressing the pharmacological issue with combined TMS–fMRI, Li et al. (2004b) compared in a randomized, double-blind crossover study the TMS-evoked activity patterns revealed by fMRI before and after administration of single doses of Lamotrigine (LTG), a use-dependent sodium channel inhibitor, versus placebo (Fig. 6). First, the authors confirmed that LTG significantly reduced corticospinal excitability, in line with previous electrophysiological TMS studies (Ziemann et al. 1996, 1998). They then showed that LTG administration reduced 1 Hz rTMS-evoked activity changes in primary and secondary motor regions compared to the placebo condition. Interestingly, LTG had the opposite effect on connections activated by rTMS of prefrontal cortex. There, LTG increased the TMS-evoked activity changes in orbitofrontal and hippocampal areas (Li et al. 2004b). This study provides a first example that combined TMS–fMRI can be used to characterise how inter-regional effective interplay may change following administration of neuroactive compounds. In addition it shows that the effects of pharmacology upon remote effects of TMS may not necessarily generalise across different TMS target regions.

In the future, an analogous combined TMS–fMRI approach could chart potential changes in inter-regional interplay during disease, and test whether this responds to novel treatments. For example, initial work suggests that combined TMS–fMRI can measure the functional connectivity of contralesional premotor cortex following stroke

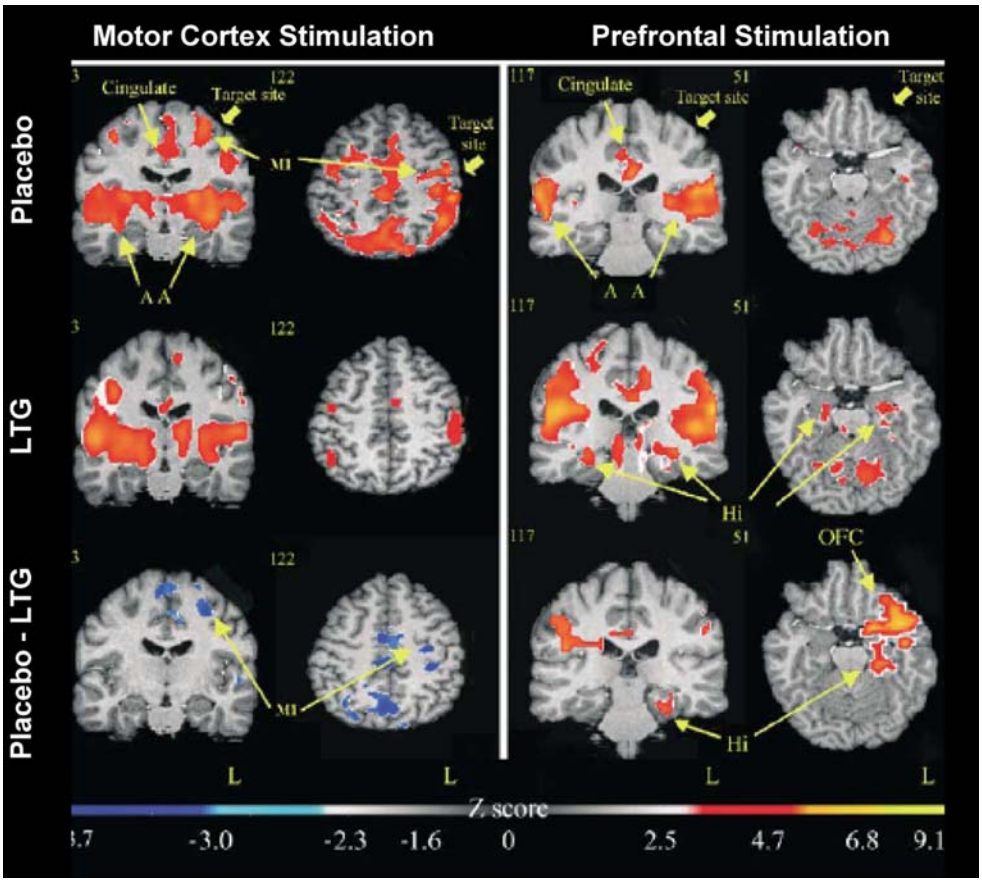

Fig. 6 Concurrent TMS–fMRI for mapping causal interactions in disease. In a randomized, double-blind crossover study, TMS-evoked activity was studied before and after administration of Lamotrigine (*LTG*) or placebo. One hertz of TMS was applied to either left motor cortex or dorsolateral prefrontal cortex. The most important finding was that TMS-evoked activity was influenced by LTG administration, but critically this influence depended on the TMS stimulation site. During M1 stimulation LTG led to a decrease in TMS-evoked activity, but it had an opposite impact for activity evoked by prefrontal stimulation. In the latter case, activity during TMS increased in limbic structures after LTG administration, compared to placebo. The results illustrate how concurrent TMS–fMRI can reveal TMS-evoked activity changes and their interaction with neuroactive drugs. Such approaches may provide critical new insights about therapeutic applications of TMS, by revealing the target site-specific impact of stimulation on activity across the entire brain, and its pharmacological modulation (adapted from Li et al. 2004a)

(Swayne et al. 2006), and shows how this may relate in individual patients to the size of the initial lesion. Viewed in this way, TMS–fMRI holds promise as a method for studying the remote influences of a particular brain region during pathology, and may thereby inform and guide possible therapeutic applications for TMS.

It is in principle also possible to study specific causal interactions and remote TMS–fMRI effects even within single patients. Bestmann et al. (2006) provide a recent example, when they studied an amputee patient with persisting phantom-limb experiences for the missing lower arm and hand, 3 years after amputation. In some patients, phantom-limb experiences may be induced using TMS (Mercier et al. 2006), and the emergence of such TMS-evoked perceptual phenomena may require concerted interplay among several brain regions. Single TMS pulse applied to the putative former M1 hand area reliably elicited a conscious sense of movement (SoM; or phantom twitch) for the phantom hand. In order to determine which brain areas contributed to the conscious sense of movement for this single case, the TMS intensity was set such that if produced illusions of movement on 50% trials when applied during fMRI. It was then possible to separate out trials with and without a conscious SoM, and ask which areas were activated differently following the TMS. Any differences that emerged could not be due to differences in the noise of the TMS or the scalp sensation produced. Furthermore, no movements were evoked at this intensity, not even in proximal muscles. The analysis revealed activity increases not only in stimulated M1, but also PMd, anterior intraparietal sulcus, and caudal SMA for trials with versus without a perceived SoM (Fig. 7). These brain regions are also involved in illusory hand movements in normals (Naito et al. 1999; Naito et al. 2002; Romaiguere et al. 2003) and motor imagery (Lotze et al. 1999; Rosen et al. 2001). This provides some support for proposals that a conscious sense of movement for the hand might arise from activity within corresponding motor-related cortical structures, even in the absence of reafferent feedback from hand muscles. But for the present purposes, the key point is that a conclusion could be reached from applying TMS–fMRI within just a single case, thus further illustrating the potential of the combined TMS–fMRI methodology.

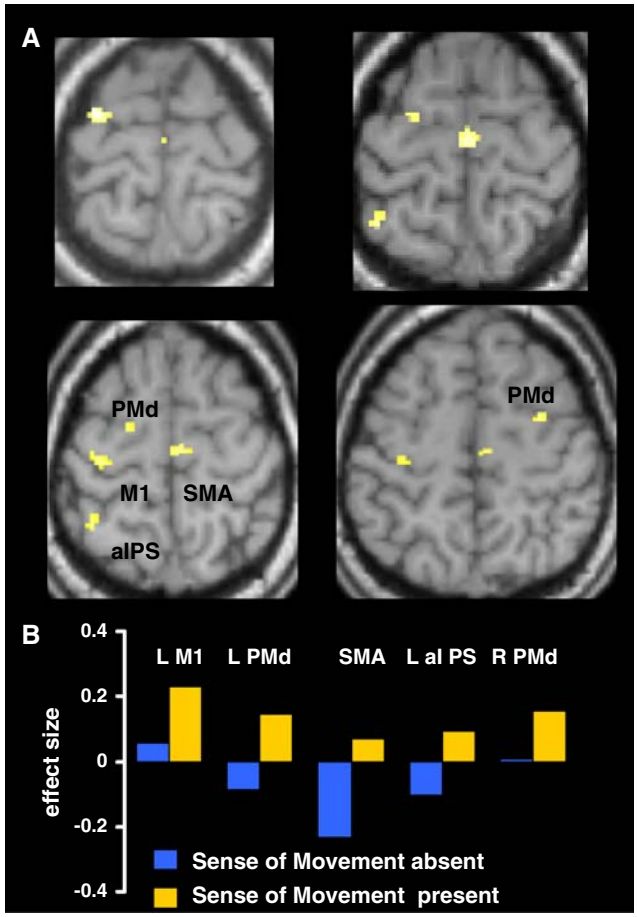

Fig. 7 Using concurrent TMS–fMRI for mapping the cortical correlates of TMS-evoked sense of movement (*SoM*). **a** Activity changes for the comparison of trials with versus without a phantom SoM, at the same intermediate TMS intensities, in an amputee patient experiencing TMS-evoked phantom movements of her missing hand. When a conscious phantom SoM was perceived in response to a TMS pulse applied to the putative hand region of M1 contralateral to the amputation, activity increases were observed in several motor-cortical regions, including the stimulated (left) M1, left and right PMd, left anterior intraparietal sulcus (*aIPS*), and caudal SMA. Importantly, TMS did not evoke muscle movements in contralateral proximal arm muscles. **b** fMRI percent signal change from these five motor-related regions (left M1, left and right PMd, SMA, left aIPS), for trials with or without evoked phantom SoM experienced, *at the same level of TMS intensity* (adapted from Bestmann et al. 2006)

Controlling for non-specific effects of TMS

In addition to the neural stimulation effects that it can induce, TMS can also give rise to auditory sensations, somatosensory and tactile stimulation, or potential startle effects. These effects depend upon parameters such as the intensity, frequency and site of TMS. Controlling for them requires carefully designed experiments and subsequent analyses.

The main source of the non-specific effects of TMS is due to the resulting Lorentz forces arising in the stimulation coil windings. These lead to brief but strong mechanical forces, resulting in small vibrations that produce an intense and clearly audible "click" sound. Multiple studies combining TMS and neuroimaging (PET, fMRI, EEG) show activity increases in auditory and somatosensory brain regions, which can be attributed to these secondary effects (Baudewig et al. 2001b; Bestmann et al. 2003; Bohning et al. 1999, 2000b; Nikouline et al. 1999; Siebner et al. 1999). In addition, reflexive responses such as eye-blinks or pupil dilation may be triggered when the TMS coil is discharged,

additionally complicating the interpretation of evoked activity changes.

One way of excluding such potentially confounding effects is to use appropriate control sites. This approach will succeed if the non-specific effects of TMS remain constant whereas TMS-evoked functional changes on brain activity depend on the specific function and connectivity of the stimulated cortical region (Baudewig et al. 2001b; Kemna and Gembris 2003; Ruff et al. 2006, 2008a, b; Sack et al. 2007). For example, Sack et al. (2007) compared stimulation of left versus right IPS, during a visuospatial judgement task. As only TMS to the right parietal cortex impaired visuospatial task processing, non-specific stimulation effects were ruled out. Using a similar approach, Ruff et al. (2006) compared TMS-evoked changes in BOLD activity for right FEF versus vertex. In their study, activity changes in visual cortex were specific to FEF stimulation, whereas there was no difference in auditory cortex activity for FEF- versus vertex-TMS. In addition, the authors included blinks and pupil dilations as regressors in their statistical model, thereby accounting for any responses in visual cortex due to these possible nuisance effects (Ruff et al. 2006, 2008a, b).

The use of factorial experimental designs can also help to control for non-specific stimulation effects, by testing for interactions between different stimulation parameters (e.g. time of stimulation, or stimulation intensity) and task condition (e.g. absence or presence of a visual stimulus, or task performance vs. rest); see Bestmann et al. 2008a, b. A further approach is the use of identical TMS intensities which on some trials lead to a conscious perception, such as a visual phosphene or a sense of movement. One can then directly contrast trials with versus without such a conscious perception, while controlling for TMS input (cf. Bestmann et al. 2006). When using the "virtual lesion" approach, one needs to take into account behavioural differences across experimental conditions that might otherwise trivially explain differences in activation patterns or amplitudes. This can be achieved by explicitly modelling behavioural responses, such as reaction times, movement onset and duration, or subjective experience. But one powerful aspect of combined TMS–fMRI is to chart interregional influences across the brain which do not necessarily require a behavioural perturbation, and can simply be assessed when applying TMS during different activation states without disrupting any behaviour (Bestmann et al. 2008b; Ruff et al. 2008a).

Conclusions and future directions

Combining TMS concurrently with neuroimaging holds great promise for studying causal interplay in the human brain. Moreover, this can potentially provide unique insight into the neuronal underpinnings and dynamics of TMS effects, across the whole brain. Highlighting activity changes beyond the stimulation site is a considerable asset, as it can enhance our understanding of the interactions between remote but interconnected brain regions. As illustrated in this review, understanding these remote TMS effects can help to generate new hypotheses regarding the mechanisms by which TMS disrupts or improves task performance. Applied in this way, combined TMS–fMRI provides information that complements other approaches, such as double-coil TMS, motor-evoked potentials, or TMS combined with EEG, PET, or NIRS. A more complete picture of the neural underpinnings of TMS and how these interact with cognition, behaviour and pathology can only be accomplished using such complementary approaches together.

Other neurostimulation techniques that can be safely applied in healthy humans can provide complementary tools to map out causal interactions in the human brain. For example, transcranial electric stimulation (TES) activates neural structures in a similar way as TMS, and its basic physiology has been investigated in both human and animals. It can therefore complement TMS–fMRI by comparing TES-evoked activity changes with those evoked by TMS. Combined fMRI-TES has recently been applied to study interactions in the motor (Brocke et al. 2007) and visual (Brandt et al. 2001) systems. Another neurostimulation technique is transcranial direct current stimulation (tDCS). This applies low-amplitude direct currents via scalp electrodes (Nitsche et al. 2003; Nitsche and Paulus 2000), which are thought to modify transmembrane potentials in neurons. These may lead to changes in excitability and neural firing rates for large regions of cortex that may outlast the stimulation for minutes or hours. Initial studies show that the combination of tDCS and fMRI is technically feasible (Baudewig et al. 2001a). While tDCS may be less focal compared to TMS, it may be of particular importance for its therapeutic applications, and mapping out its impact on activity throughout the brain may provide important insight into large-scale activity changes during or following tDCS.

Physical perturbation of a targeted cortical region, as with TMS, is not the only approach to test for interplay between human brain regions. Other approaches, in fMRI research without TMS, provide mathematical models that can be used to assess possible changes in "effective connectivity" between brain regions under different conditions (Friston et al. 2003; Patel et al. 2006; Penny et al. 2004a; Roebroeck et al. 2005; Stephan et al. 2005; Worsley et al. 1998). For example, dynamic causal modelling (DCM) can test for possible changes in effective connectivity due to experimental manipulations in fMRI data

(Friston et al. 2003). DCM combines a model of the hidden neuronal dynamics with a forward model that translates neuronal states into predicted measurements. The TMS–fMRI studies we have reviewed above typically did not utilize such sophisticated fMRI analyses, instead simply treating the TMS manipulation as a standard event-related or blocked factor. Even this simple approach was notably able to reveal causal influences of the targeted brain region on other remote interconnected areas that could vary in a state-dependent manner. But in principle, further analysis approaches such as DCM could model the TMS input to a given cortical region, and directly compare model predictions against the fMRI data obtained to assess causal interregional influences. Moreover, the fusion of different methods for studying effective connectivity can allow new hypotheses to be tested that otherwise would be difficult to address. For example, the recent development of non-linear DCMs (Stephan et al. 2008) together with Bayesian model selection (Penny et al. 2004b) now allows us to address the question of whether the impact of TMS at the stimulation site influences activity in remote (and putatively interconnected) regions via direct connections, or via intermediate interconnecting areas. In a situation where applying TMS to area A changes activity in area B, via DCM (and Bayesian model selection) one might test whether this reflects a direct influence, or an indirect pathway via another interconnecting region C, for example. The development of models of effective connectivity that combine (non)linear neuronal state equations with hemodynamic forward models, as in DCM, provide interesting prospects for assessing computational models of effective connectivity with new perturbation approaches such as concurrent TMS–fMRI.

In closing summary, over the past two decades TMS has informed our understanding about causal relationships between brain function and behaviour in the human brain. Future understanding of TMS, and of brain–behaviour relations in non-invasive human studies may, however, critically depend upon identifying the impact of TMS across the brain in more detail, including causal influences of TMS upon remote brain regions interconnected with the targeted site. Establishing causal brain–behaviour relations in the healthy brain via TMS requires charting of the activity changes elicited by TMS not only in the local targeted site, but also for remote and interconnected brain regions, and of how these remote changes may vary with state. One promising way to achieve this in human studies is by combining TMS with fMRI. As understanding of causal interplay between human brain regions increases, stimulating new questions will emerge, and can be further approached using increasingly sophisticated methodological combinations.

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