Behavioural Brain Research 191 (2008) 141–147

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

Combining TMS and EEG to study cognitive function and cortico–cortico interactions

Paul C.J. Taylor[a,*], Vincent Walsh[a,b], Martin Eimer[a]

[a] The Henry Wellcome Building, School of Psychology, Birkbeck College, Torrington Square, London WC1E 7HX, UK
[b] Institute of Cognitive Neuroscience, Department of Psychology, University College London, 17 Queen Square, London WC1N 3AR, UK

ARTICLE INFO

Article history:
Received 3 March 2008
Accepted 26 March 2008
Available online 1 April 2008

Keywords:
Transcranial magnetic stimulation
Electroencephalography
Attention
Frontal eye fields
Medial frontal cortex

ABSTRACT

There has long been an interest in exploring the functional dynamics of the brain's connectivity during cognitive processing, and some recent methodological developments now allow us to test important long-standing hypotheses. This review focuses on the recent development of combined online transcranial magnetic stimulation and electroencephalography (TMS–EEG) and on new studies that have employed this combination to study causal interactions between neural areas involved in perception and cognition.

Contents

1. Why combine TMS and EEG? When "*when*" is important

Transcranial magnetic stimulation (TMS) uses an electromagnetic coil which is placed on a subject's scalp and through which a brief current is passed that typically reaches its peak within 200 μs and returns to zero within approximately 1 ms. The rapidly changing magnetic field induces an electric current in the underlying nervous tissue, and thereby usually disrupts the normal pattern of activity with what has been called "neural noise" [1,2]. While early coils were circular [3], the now-standard 'figure-of-eight'-shaped coil ensures that the maximum impact on cortical neurons is directly underneath the coil's centre. Analogous to the use of lesions or microstimulation in animals or in patients, TMS enables the cognitive neuroscientist to manipulate cortical activity directly, and to study the consequences on behaviour. For example, if TMS is applied at a high enough intensity to the hand area of primary motor cortex (M1) then a hand-twitch is elicited, measurable with electromyography (EMG) as a motor-evoked potential (MEP [3]). Although the nearby dorsal premotor cortex (PMd) is connected monosynaptically with M1, PMd TMS does not elicit a twitch [4]. Similarly, when area V5/MT is stimulated at sufficient intensity then the blindfolded subject may perceive a moving phosphene, but TMS to the frontal eye field (FEF) has no such effect [5]. The fact that TMS applied to PMd or FEF has no immediate perceptual or motor effects does not imply that TMS cannot be used to uncover the functional role of these areas. Generally, for any area that is close

* Corresponding author. Tel.: +44 2076316522; fax: +44 2076316587.
E-mail address: pc.taylor@bbk.ac.uk (P.C.J. Taylor).

0166-4328/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2008.03.033

enough to the scalp to be affected by TMS (including those areas for which there are no immediate TMS-induced phenomena), TMS followed by the measurement of the pattern of behavioural disruption can be used to infer cognitive function, provided that appropriate experimental designs are used. While imaging methods may record a pattern of neural activity that correlates with the performance of a task, the utility of TMS as a lesion method lies in the causal nature of the inferences that can be made on the basis of its effects.

The application of TMS that is the focus of this review is its use in the study not only of the function of one brain area, but also of the way in which that area affects others. TMS has its main, direct effects underneath the coil (the usual target of stimulation), but it also has secondary effects on areas connected to the target site. One way to investigate such interactions is to look at how stimulation with one coil changes the effects of subsequent stimulation with a second coil. For example, with one coil placed over M1 to elicit MEPs and another over dorsal PMd, application of an additional TMS pulse to PMd 10 ms before the pulse to M1 results in a reduction of MEP amplitude [6]. PMd TMS does not simply mimic the effect of TMS to M1, to which it is strongly connected, but has a different, modulatory role. Similar dual-site effects have also been demonstrated in the visual system: FEF TMS does not elicit phosphenes as seen with TMS to V5, but a pulse of TMS to the FEF can make it easier to produce a phosphene if V5 is stimulated 20–40 ms afterwards [5]. With most sites, however, TMS does not have such an experimentally useful outward manifestation on resting subjects. In these cases, using TMS to study cortico–cortical interactions, and specifically the effect of TMS to one area on remote but interconnected areas, requires TMS to be combined with some concurrent measure of brain activity. In order to find out where activity spreads to after TMS, TMS has been combined online with PET and fMRI [7–12]. When timing is important, TMS can be combined with electroencephalography (EEG). In this review it is argued that combined online TMS–EEG can offer insights into how neural areas interact during cognition, allowing us to not only to study the causal role of specific brain areas in behaviour, but also, and most importantly, when and how activity in one area affects activity in other areas.

2. Technical and methodological constraints and considerations

EEG signals represent the temporal profile of the change in the potential difference between two electrodes placed on the scalp. The EEG obtained on several trials can be averaged together time-locked to the stimulus to form an event-related potential (ERP). Alternatively, the frequency content of the EEG signal can be analyzed. Whereas PET and fMRI rely upon the sluggish haemodynamic response occurring after increases in neural activity, it is the brain's own electrical activity that directly drives the EEG signal, bestowing it with its high temporal resolution. EEG recording systems amplify the small changes in voltage which are detectable through the skull and scalp. Until relatively recently, the extreme sensitivity of EEG amplifiers also meant that if a TMS pulse was discharged within a few centimeters of the recording electrodes, a huge long-lasting artifact occurred in the EEG signal. The sudden surge in current after a single pulse would overload and saturate conventional recording equipment, so that the amplifier was rendered unusable for seconds, or even permanently. Two developments in EEG amplifier technology now enable avoiding this saturation. It is now possible to rapidly stop and restart EEG recording around the time of the TMS pulse (referred to as the 'clamping' or 'sample-and-hold' method), thereby preventing amplifier saturation. More importantly, recent improvements in the ability of DC amplifiers to deal with the surge in charge now allow for continuous EEG recording during TMS without long-lasting or permanent amplifier saturation. With either technique, the black-out period immediately after the TMS pulse where the TMS discharge artifact prevents the acquisition of meaningful EEG data can now certainly be reduced to less than 40 ms, and some systems even report recovery times between 2 and 20 ms after TMS [13]. Advances in software development now aid artifact removal after acquisition [14]. In addition to innovations in amplifier technology, it has recently been suggested that the size of the TMS artifact can be reduced if pinpricks are applied to the scalp under the EEG electrodes beforehand [15].

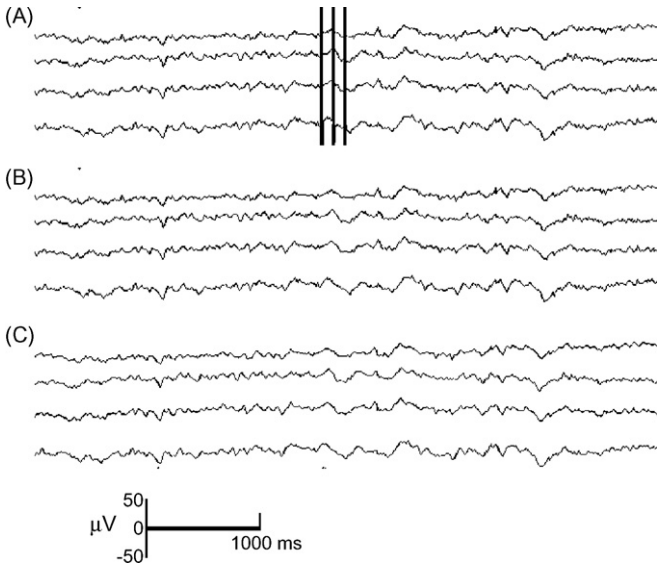

Fig. 1. (A) Raw EEG data from four occipital electrodes showing the TMS artifact when three pulses at 10 Hz are applied to the right frontal eye field; (B) the same dataset after artifacts are removed and data are extrapolated for the 40 ms time-window after each pulse; (C) after artifact removal the data can then be filtered. Unpublished raw data from ongoing experiments by the authors.

It is important to stress that filters must not be used during recording because these interact with the residual spike-shaped artifact leading to a ripple in the signal after each TMS pulse that can last for up to a second. Filters can be used after recording once the TMS discharge artifacts have been removed from the data (Fig. 1). A more mechanical but equally important part of methodological procedure is to avoid physical contact between the coil and conventional recording electrodes, because this will induce further high- and low-frequency noise, which would need to be filtered out. Although the cap on which EEG electrodes are worn is made of fabric only a fraction of 1 mm thick and thus does not noticeably weaken the cortical effects of TMS, the possibility that TMS efficiency is reduced needs to be taken into account when thick EEG electrodes are used and the distance between coil and scalp is increased further.

TMS also induces tactile and auditory artifacts which must be controlled for. At the same time as affecting neural activity, each TMS pulse also transiently activates the muscles in the underlying region of scalp, creating a light knocking or twitching sensation. There is also a loud click due to the fractional but rapid movement of the component wire within the coil as each pulse is delivered. In order to control for this acoustic and somatosensory stimulation, the effects of stimulating the active area in a study are usually contrasted with a control site. This is especially important in combined TMS–EEG studies in order to disentangle the changes in EEG and ERP signals that reflect neural activity caused by the magnetic stimulation from those evoked by the accompanying sensory stimulation.

3. Spatial and temporal resolution

The temporal resolution of TMS is theoretically limited only by the duration of the TMS pulse (approximately 1 ms). Likewise, the temporal resolution of EEG is limited by sampling rate, and EEG data are now usually acquired at 1000 Hz. But the temporal resolution of the combined TMS–EEG method is determined not only by the nature of the component techniques but also by their interaction. As discussed above, it can take several milliseconds for the amplifier to reset after TMS is applied. It can also take some time for any given pattern of neural activity to generate a signal that is detectable at the scalp. This is because EEG is sensitive not only to the firing rates of the underlying neural activity but also to the synchrony of the activity, and the geometry of the active neural elements. Therefore, the latency of a change in neural activity recorded with EEG provides an upper limit of the time-point that a neural event started. For any EEG effect that is observed after a TMS pulse, one can conclude that there was a change in neural activity that started either slightly before or synchronous with the observed EEG effect.

The spatial resolution of the inference that TMS–EEG can afford is also affected by the way that the two techniques interact. If the immediate spatial resolution of TMS is considered to be the minimum change in coil position which can elicit different measurable behavioural effects then this can be taken to be less than 1 cm, as illustrated by the small shifts in coil position that can produce or eliminate MEPs or phosphenes. As for EEG, the immediate spatial resolution is low (on the order of centimetres), because single electrodes usually pick up changes in activity that originate from a large volume of brain. Incorporation of TMS into an EEG experiment, however, can potentially boost this spatial resolution by demonstrating that a specific EEG effect is affected by TMS over a cortical region, from which it can be inferred that the stimulated area is – either directly or via remote connections – involved in generating the pattern of neural activity indexed by that EEG effect. In some cases it has been established through combination with other converging methods that the difference between the EEGs recorded on two experimental conditions can be reliably related to activity in a distinct cortical region [such as the lateralised readiness potential and M1, see 16]. Additionally some spatial resolution can be tentatively restored through mathematical modeling of the most likely arrangement of neural generators that could have produced the recorded pattern (source localization analysis).

4. TMS–EEG studies in the time domain

In the last decade there has been rapid growth in the use of TMS–EEG to explore the dynamics of the brain at rest [17]. These studies have explored how the consequences of TMS differ according to the context in which it is applied, and several types of context have been manipulated. For example, the use of patients with focal lesions can reveal the latent contribution made even by those deep subcortical areas that are neither accessible with TMS nor detectable in the ERP. Such a manipulation was employed in the seminal paper by Ilmoniemi et al. [13], who were the first to combine multi-channel EEG recordings with TMS (using the sample-and-hold technique, see above), to record the temporal profile of the ERP elicited after TMS of either visual cortex or M1. In normal resting subjects, the TMS-induced activity spread to the contralateral homotopic area within 20 ms.

Another type of context that can be manipulated in resting subjects is the level of arousal: after TMS to premotor cortex, the spread of the TMS-induced ERP disruption is greater when subjects are awake than when they are in non-REM sleep [18]. Resting subjects can be shown stimuli and the resulting changes on cortical connectivity can be measured. Thut et al. [19] applied single pulses of TMS to the left occipital pole while subjects passively viewed visual stimuli, finding changes in the topography of the visual-evoked potentials (VEPs) only when TMS was applied at the latency of the peak of one of the early VEP components, the P1, at 118 ms after visual stimulus onset.

While these studies investigated TMS–EEG effects with resting subjects in the absence of a concurrent cognitive task, other recent studies have used TMS–EEG to study the effect that TMS has on underlying cortex while subjects are engaging actively in a task. Fuggetta et al. [20] tested whether parietal TMS could be shown to have within-trial effects on the EEG recorded at underlying parietal electrodes when subjects performed a visual search task (with filters used to remove the artifact caused by the coil resting on the recording electrodes). Analysis focused on the N2pc ERP component, which is an electrophysiological marker of attentional target selection in a visual search task. The N2pc is obtained by calculating the difference between the ERP waveforms at lateral posterior electrodes contralateral as opposed to ipsilateral to the visual field where the search target is presented. Single pulses of TMS were applied to the right posterior parietal cortex at 100 ms after the onset of the visual search array. TMS not only delayed response times to targets during conjunction search, but also eliminated the early phase of the N2pc component (assumed to reflect the initial focusing of attention onto target locations) over the right hemisphere. In contrast, the N2pc was unaffected when TMS was delivered to a control site (vertex). This finding demonstrates that rPPC TMS interferes with attentional selectivity in remote visual areas, and thus by extension that the PPC has a causal role in the attentional selection of targets in visual search. One way to extend such work is to continue the use active of tasks but investigate what the consequences of TMS to an area are on other, distant, areas.

5. Using TMS–EEG to investigate the role of the FEFs in attentional selection

In this section, the use of TMS–EEG for the investigation of cortico–cortical interactions will be illustrated in more detail by presenting a recent study [21] that explored the role of the FEFs in attentional selection. The FEF is part of the frontal–parietal–medial circuit of areas revealed in many imaging experiments to control the orienting of visual spatial attention [for a meta-analysis see 22]. During the cueing period of attentional tasks there are increases in the activity in both FEF [23] and in visual cortex [24] even during the time in which there are no visual stimuli being presented. TMS of the FEF disrupts performance at tasks requiring visual spatial attentional selection [25,26] with the timing of effects consistent with the FEF acting to affect the visual cortical activity. Previous studies where TMS was combined with PET have revealed that FEF TMS activates a network of areas including visual cortex while subjects had their eyes closed [7]. Along similar lines, combined TMS–fMRI has shown that this distal effect of FEF stimulation on posterior visual areas is independent of whether subjects passively view visual stimuli [12].

If FEF TMS has direct effects on visual cortex, these effects should also be visible with EEG measures. While the effect of attention on visual cortex has been well characterised with ERPs [27], what is lacking is any direct evidence that the FEF interacts with visual cortex during these tasks. Taylor et al. [21] exploited the temporal resolution of TMS–EEG to test for the causal interaction between these areas during performance of an active task, exploring whether the FEF affects visual activity during attentional selection as implemented in the classic rule-guided or 'endogenous' visual spatial attentional task [28]. Centrally fixating subjects were presented with a central arrow pre-cue embodying either the rule to 'attend left' or 'attend right'. Successful attentional deployment

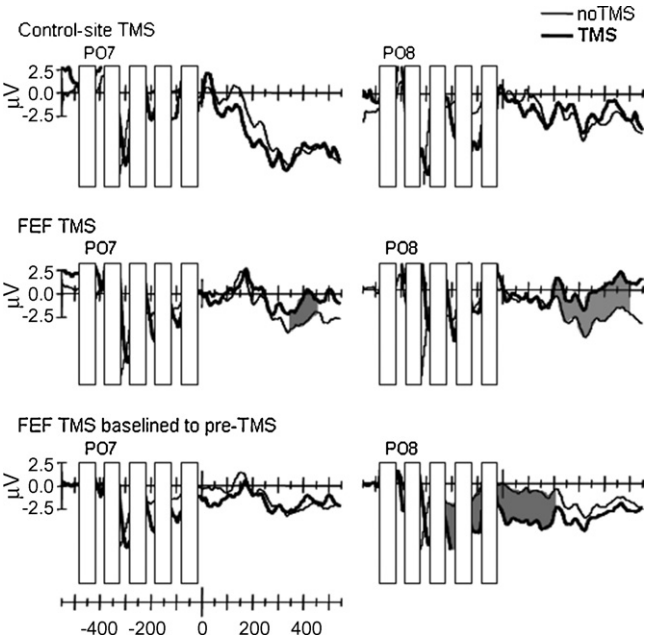

Fig. 2. Effect of right frontal eye field TMS on visual cortical activity during endogenous visual spatial attentional orienting. At time −500 a central arrow cue was presented, indicating the likely position of the upcoming peripheral target at time 0. Starting 50 ms after this a train of five pulses of 10 Hz TMS was applied, leading to blanking of the signal for less than 40 ms (white boxes). TMS of a control site (top) had no effect on the ERP recorded during valid trials. After FEF TMS (middle) there was a negative deflection (difference shaded grey) that was more pronounced at electrode PO8 over right visual cortex, ipsilateral to the TMS, than at PO7 overlying left visual cortex. When this data was re-baselined to the period immediately before the TMS started (bottom), the effect of TMS can be seen to start after the third TMS pulse and to remain until 200 ms after onset of the visual stimulus. From Taylor et al. [21].

was shown by enhanced behavioural performance at discriminating visual stimuli presented on the indicated side (valid trials) relative to a smaller proportion of trials on which the upcoming stimulus was presented on the unexpected side (invalid). In addition, comparison of valid and invalid trials yielded the consistent differences on ERPs shown previously to be governed by selective attention. These stimuli were then used in a combined TMS–EEG experiment in which five pulses of 10 Hz TMS were applied to the right FEF in the cue-target interval, starting 50 ms after cue onset and ending 50 ms before the target. Participants detected the small fraction of validly cued stimuli that were targets, a manipulation that boosts the attentional modulation seen over visual electrodes [27]. The position of the FEF was first verified anatomically by co-registration to each subject's MRI scan, and then tested functionally, where a similar TMS protocol was shown to impair centrally cued overt eye movements. The effective spatial resolution of the EEG recording was increased by re-referencing the signal recorded from electrodes over visual cortex to an immediately adjacent electrode, emphasizing activity in the immediately underlying cortex. TMS of the right FEF caused a within-trial modulation of activity in the right visual cortex, evident as a protracted shift in the baseline of the ERP (Fig. 2). The temporal resolution of EEG enabled showing that this effect started within approximately 190 ms after cue onset, during the cue-target interval and before the visual stimulus was presented. This interaction was not eliminated by the presentation of an attended stimulus but continued until 200 ms after visual stimulus onset, which includes the time in which it has been shown that attention normally modulates visual activity. None of the effects of FEF TMS either on visual activity or on oculomotor control occurred during TMS of a somatosensory control site. In addition to adding causal weight, temporal resolution and cognitive context to the interaction that has been postulated to exist between FEF and visual cortex, these results also suggest that such within-trial distal effects on visual cortex would have co-occurred with the other effects of FEF TMS that have been described, whether disrupted behavioural performance on visual attentional tasks [25,26], or the physiological effects shown through combining TMS with other methods [5,7,12]. It also illustrates the contribution that the methodological development of TMS–EEG offers, demonstrating the consequences that TMS to one area has on functionally connected areas while subjects perform a task hypothesized to require that connection—in this case the role that FEF plays in modulating visual cortex when subjects covertly orient their selective visual spatial attention. The temporal resolution of EEG is particularly revealing of the consequences of TMS when subjects perform an active task, because the time course of the TMS effect on the EEG can be related to the time course of the ongoing cognitive processes.

6. Using TMS–EEG to study the role of medial frontal cortex in motor control

Online TMS–EEG can also be exploited when different task conditions are compared, enabling recording of how the strength of the connection between areas varies according to the cognitive demands, mapping the dynamics of functional connectivity. One ongoing debate in which functional connectivity is crucial involves the role of the medial frontal cortex (MFC) in the voluntary control of action. Several studies using various stimuli have reported that the MFC is active on those trials where the need for action selection is increased [29,30]. One way in which such a role is sometimes framed is in terms of detecting the conflict between the alternative response options presented, and then sending this information to other areas to be resolved on the following experimental trial [31,32]. In addition to or instead of conflict monitoring, it is also possible that the MFC take an active role in directly selecting between the alternate actions that are represented downstream in motor cortex, and that this interaction occurs within the experimental trial on which different options must be weighed against each other. Here the critical issue in the debate over the function of an area is explicitly about the time-course with which it interacts with other areas, and is therefore a prime example of a question amenable to the combined TMS–EEG approach.

To address this question, Taylor et al. [33] applied repetitive TMS to the left MFC, in trains of three pulses at 10 Hz, with the middle pulse presented simultaneously with the onset of an array of 'flanker' stimuli which provide the opportunity to experimentally manipulate action selection [34]. The task was to discriminate as quickly as possible whether the central arrow in an array is pointing to the left or to right, responding with the left or right hand. Responses were slower and/or less accurate if the peripheral flanking arrows point in the incongruent than the congruent direction relative to the important central arrow. This experimental manipulation of action selection has a robust ERP correlate—modulation of the lateralised readiness potential [LRP, 16]. This potential can be derived from electrodes overlying the left and right primary motor cortices by subtracting the activity recorded from the electrode ipsilaterally to the responding hand from the contralateral waveform. This is averaged across hands and can be demonstrated theoretically as well as empirically with intracortical recordings to provide a refined measure of activity in M1. The LRPs to congruent and incongruent trials differ from each other in accordance with this—the incongruent waveform peaking later as it takes longer for the correct primary motor cortex to be activated by the higher-level motor systems. TMS–EEG was used to test for a functional link where the MFC acted down on M1 to select the appropriate action. Left MFC TMS increased the congruence effect on the LRP, with

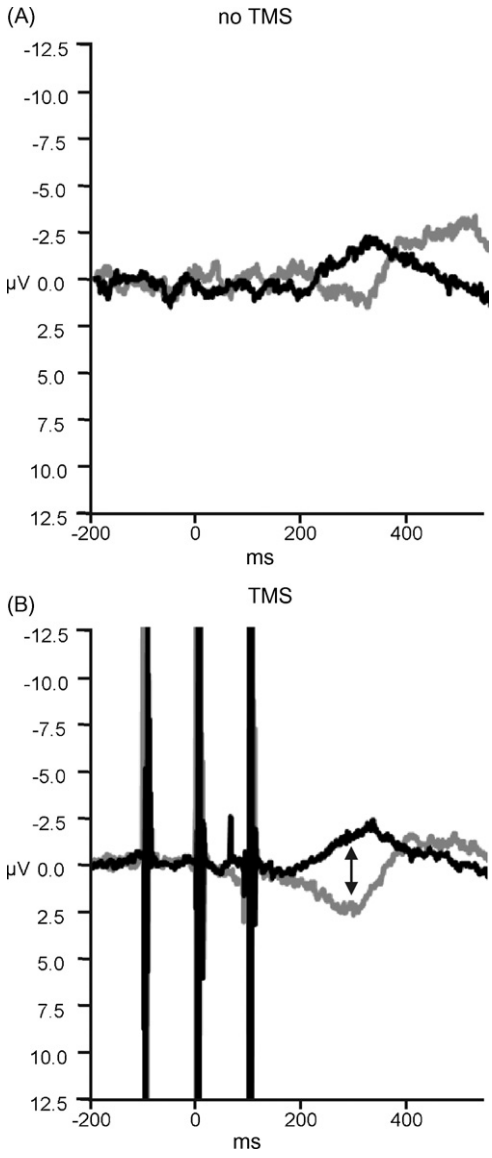

Fig. 3. Effect of left medial frontal cortical (MFC) TMS on the lateralised readiness potential (LRP), a measure of activity in primary motor cortex (M1): (A) on no TMS trials during a flanker task, the LRP on congruent trials (black waveform) peaks earlier than that on incongruent trials (grey); (B) after medial frontal TMS (visible as large spikes) there is an increased congruence effect, due to a worsening of performance on those incongruent trials in which the demands for action selection are greatest. MFC activity is therefore shown to have a within-trial effect on the activity in a distal area, M1, which varies according to the task. From Taylor et al. [33].

the difference between congruent and incongruent trials starting 80 ms earlier than without TMS (at 200 ms after stimulus onset) and lasting until 360 ms (Fig. 3). This was due to a specific effect on incongruent trials, with the LRP being shifted further away from the congruent waveform, in the direction consistent with continued uninhibited activation of the incorrect response plan. The effects of TMS on behaviour and on the LRP showed a correlation where subjects whose incongruent waveform was deflected the most by TMS also showed the greatest worsening of performance after TMS on incongruent trials. Separating out the ERPs according to which hand was being responded with showed that TMS of the left MFC only affected incongruent trials when the right hand was being used to respond. Such hand specificity also supports a role of MFC beyond merely monitoring the presence of response conflict since it is only after conflict has been flagged and the correct hand is being selected that any effect could be hand-specific. None of these effects occurred after TMS to a more posterior control site that has not been suggested to play a critical role in action selection. This provides evidence that during action selection the MFC interacts with downstream motor cortex, picking the correct action plan out from the conflicting options available, within the same experimental trial in which they are presented.

7. TMS–EEG in the frequency domain

In addition to analyzing EEG data in the time domain, several studies have investigated whether TMS can also alter the spectral content of the EEG signal. Oscillations at different frequencies may play an iterative role in cognitive processes such as attention [35]. There is some evidence that TMS can elicit changes in the power of oscillations in the EEG signal at specific frequencies. M1 TMS increases the power of the beta-frequency band (15–30 Hz) recorded from adjacent electrodes [36]. TMS–EEG can investigate whether the neural mechanisms indexed by these frequency changes have any causal functional role. The beta-frequency oscillations after M1 TMS are of smaller amplitude in patients with unilateral damage to the ventrolateral nucleus of the thalamus when the affected hemisphere is stimulated, compared to the intact hemisphere [37]. Effects on oscillatory patterns in the EEG, whether in the beta or alpha (approximately 7–12 Hz) frequency bands, have been framed in terms of cortical excitability. In motor cortex, excitability can be measured as the amount or intensity of TMS required to elicit an MEP. When the cortex is at its least excitable, for example, during sleepiness or sleep, MEP amplitudes are reduced [38]. In awake, resting subjects TMS-induced MEPs are also smaller if subjects close their eyes, a simple manipulation which increases alpha power [39]. The effect of M1 TMS on the alpha power increases with the intensity of stimulation [40], and the number of pulses administered and the latter effect correlates with the reduction in MEP size [41]. Although the effect on the EEG after single pulse M1 TMS may be in some cases more subtle than the large effects after cognitive manipulations [40], TMS-induced EEG effects on resting subjects can be shown at surprisingly low TMS intensities, and in a fashion that varies with stimulation site, stimulation intensity and pharmacological challenge [for a recent review see 17]. TMS studies of primary motor cortex often exploit the unique nature of the MEP as an outward signal of the state and excitability of the motor cortex. The reported presence or absence of phosphenes after visual cortical stimulation has also been argued to reflect visual cortical excitability. In a similar way to how MEP size varies with the alpha power in the EEG recorded from electrodes overlying motor cortex, low pre-TMS alpha power recorded from visual cortex increases the probability of eliciting a phosphene [42], with those subjects who show the lowest alpha activity at rest having the lowest phosphene thresholds [43]. Offline occipital TMS decreases the alpha desynchronisation induced by visual stimuli [44].

8. Future work, caveats and conclusions

One ambition for TMS–EEG would be to derive a robust 'TMS-evoked potential' or TEP. This could hypothetically be used as a tool in much the same way as the MEP, as a marker for cortical excitability for the areas for which TMS does not induce as helpful a behavioural manifestation as an overt motor twitch. Studies have started to compare the ERP response of different areas to TMS [17], and it remains to be determined the extent to which the TEP differs across cortical regions. Exploring the relationship between TMS intensity and the size of the effect on the ERP [45]

could eventually facilitate predicting the effect of TMS to an area, a goal which seems less unrealistic in the light of recent successful attempts at modelling the effects of TMS on behaviour during cognitive tasks [46]. This becomes increasingly crucial as the diversity of reported TMS effects on behaviour increases. TMS can alter the after-effects induced by adaptation to grating stimuli in a manner argued to be consistent with it being the least active neurons which have the greatest potential to be disrupted by TMS [47]. Some TMS protocols even aid performance, and such 'paradoxical facilitation' effects have been conceived as resulting from the combination of the disinhibition of homotopic areas contralateral to the stimulated site, and the precise nature of the task in hand [48]. The strengths of TMS–EEG seem aligned to explore how it is that TMS may have different within-trial effects on distal areas during different task conditions. This would also benefit from developments in increasing the spatial resolution of the EEG measure in question. The probable location and function of the key generators of EEG signals have been modeled using various statistical techniques [e.g. 49,50] and TMS could be used to test the causal role of any sources that lie near enough the scalp to be vulnerable to TMS, thereby providing important constraints on the 'inverse problem' where an infinite number of potential sources could theoretically give rise to any given scalp EEG topography. In the same way as developments in amplifier hardware have enabled the evolution of TMS–EEG into a method of studying task-related changes in causal functional connectivity, future technological refinements may open up new avenues for research. If and when EEG amplifiers become widely available that can limit the TMS artifact to a few milliseconds or less, then it would be possible to distinguish between whether TMS–EEG effects were due to an immediate feed-forward connection or if they resulted only after several loops of interactions between the stimulated site and distal areas.

Some aspects of TMS or EEG can also limit the possibilities for their combination: the early VEP components, for example, are clearest from bright supra-threshold stimuli presented without masking, whereas several interesting TMS effects may rely on using dim and/or backward-masked stimuli [26,51]. Some target ERP modulations may not be due to the activity of areas which are accessible with TMS if the neural generators lie too far from the scalp, although such a distant position is not optimal for large detectable EEG signals.

The idea of functional connectivity is rooted in many classic models in cognitive neuroscience [e.g. 52,53] but the methodologies with which to study it have only recently been developed. As with all methods, results from combined TMS–EEG studies need to be interpreted within the context of results from other methods. Other stimulation-recording studies may be the most relevant. For example the link between the frontal eye fields and visual cortex has been explored with TMS-PET, revealing the full spatial extent of spread across the whole brain but without very high spatial resolution [7]: TMS–fMRI, revealing the precise spatial location of modulated visual activity in occipital cortex [12]; TMS–EEG, revealing the time-course of these effects [21]; intracranial microstimulation and recording in macaque [54,55] where stimulation can be much more focal although the tasks are constrained by those which can be taught to monkeys. TMS–EEG can now join with other multimodal endeavours to explore functional interaction in the human brain, to extend previous work on localizing functions to isolated regions.

Acknowledgements

Supported by a grant from the Medical Research Council (MRC), UK. P.T. thanks Matthew Rushworth and Kia Nobre for their previous collaboration in two of the experiments described here.

References

[1] Walsh V, Cowey A. Transcranial magnetic stimulation and cognitive neuroscience. Nat Rev Neurosci 2000;1(1):73–9.
[2] Harris JA, Clifford CW, Miniussi C. The functional effect of transcranial magnetic stimulation: signal suppression or neural noise generation? J Cogn Neurosci 2007.
[3] Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985;1(8437):1106–7.
[4] Koch G, Franca M, Del Olmo MF, Cheeran B, Milton R, Alvarez Sauco M, et al. Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. J Neurosci 2006;26(28):7452–9.
[5] Silvanto J, Lavie N, Walsh V. Stimulation of the human frontal eye fields modulates sensitivity of extrastriate visual cortex. J Neurophysiol 2006;96(2):941–5.
[6] Mochizuki H, Huang YZ, Rothwell JC. Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. J Physiol 2004;561(Pt 1):331–8.
[7] Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J Neurosci 1997;17(9):3178–84.
[8] Bohning DE, Pecheny AP, Epstein CM, Speer AM, Vincent DJ, Dannels W, et al. Mapping transcranial magnetic stimulation (TMS) fields in vivo with MRI. Neuroreport 1997;8(11):2535–8.
[9] Sack AT. Transcranial magnetic stimulation, causal structure–function mapping and networks of functional relevance. Curr Opin Neurobiol 2006;16(5):593–9.
[10] Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci 2004;19(7):1950–62.
[11] Fox P, Ingham R, George MS, Mayberg H, Ingham J, Roby J, et al. Imaging human intra-cerebral connectivity by PET during TMS. Neuroreport 1997;8(12):2787–91.
[12] Ruff CC, Blankenburg F, Bjoertomt O, Bestmann S, Freeman E, Haynes JD, et al. Concurrent TMS–fMRI and psychophysics reveal frontal influences on human retinotopic visual cortex. Curr Biol 2006;16(15):1479–88.
[13] Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Naatanen R, et al. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport 1997;8(16):3537–40.
[14] Litvak V, Komssi S, Scherg M, Hoechstetter K, Classen J, Zaaroor M, et al. Artifact correction and source analysis of early electroencephalographic responses evoked by transcranial magnetic stimulation over primary motor cortex. Neuroimage 2007;37(1):56–70.
[15] Julkunen P, Paakkonen A, Hukkanen T, Kononen M, Tiihonen P, Vanhatalo S, et al. Efficient reduction of stimulus artefact in TMS–EEG by epithelial short-circuiting by mini-punctures. Clin Neurophysiol 2008;119(2):475–81.
[16] Coles MGH. Modern mind-brain reading: psychophysiology, physiology, and cognition. Psychophysiology 1989;26:251–69.
[17] Komssi S, Kahkonen S. The novelty value of the combined use of electroencephalography and transcranial magnetic stimulation for neuroscience research. Brain Res Rev 2006;52(1):183–92.
[18] Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Breakdown of cortical effective connectivity during sleep. Science 2005;309(5744):2228–32.
[19] Thut G, Northoff G, Ives JR, Kamitani Y, Pfennig A, Kampmann F, et al. Effects of single-pulse transcranial magnetic stimulation (TMS) on functional brain activity: a combined event-related TMS and evoked potential study. Clin Neurophysiol 2003;114(11):2071–80.
[20] Fuggetta G, Pavone EF, Walsh V, Kiss M, Eimer M. Cortico–cortical interactions in spatial attention: a combined ERP/TMS study. J Neurophysiol 2006;95(5):3277–80.
[21] Taylor PC, Nobre AC, Rushworth MF. FEF TMS affects visual cortical activity. Cereb Cortex 2007;17(2):391–9.
[22] Grosbras MH, Laird AR, Paus T. Cortical regions involved in eye movements, shifts of attention, and gaze perception. Hum Brain Mapp 2005;25(1):140–54.
[23] Schall JD. Neural basis of deciding, choosing and acting. Nat Rev Neurosci 2001;2(1):33–42.
[24] Kastner S, Pinsk MA, De Weerd P, Desimone R, Ungerleider LG. Increased activity in human visual cortex during directed attention in the absence of visual stimulation. Neuron 1999;22(4):751–61.
[25] O'Shea J, Muggleton NG, Cowey A, Walsh V. Timing of target discrimination in human frontal eye fields. J Cogn Neurosci 2004;16(6):1060–7.
[26] Muggleton NG, Juan CH, Cowey A, Walsh V. Human frontal eye fields and visual search. J Neurophysiol 2003;89(6):3340–3.
[27] Eimer M. Sensory gating as a mechanism for visuospatial orienting: electrophysiological evidence from trial-by-trial cuing experiments. Percept Psychophys 1994;55(6):667–75.
[28] Posner MI. Orienting of attention. Q J Exp Psychol 1980;32(1):3–25.
[29] Brass M, von Cramon DY. The role of the frontal cortex in task preparation. Cereb Cortex 2002;12(9):908–14.
[30] Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, et al. A core system for the implementation of task sets. Neuron 2006;50(5):799–812.
[31] Rushworth MF, Walton ME, Kennerley SW, Bannerman DM. Action sets and decisions in the medial frontal cortex. Trends Cogn Sci 2004;8(9):410–7.

[32] Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn Sci 2004;8(12):539–46.
[33] Taylor PC, Nobre AC, Rushworth MF. 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 2007;27(42):11343–53.
[34] Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in nonsearch task. Percept Psychophys 1974;16:143–9.
[35] Fries P. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 2005;9(10):474–80.
[36] Paus T, Sipila PK, Strafella AP. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. J Neurophysiol 2001;86(4):1983–90.
[37] Van Der Werf YD, Sadikot AF, Strafella AP, Paus T. The neural response to transcranial magnetic stimulation of the human motor cortex. II. Thalamocortical contributions. Exp Brain Res 2006;175(2):246–55.
[38] Avesani M, Formaggio E, Fuggetta G, Fiaschi A, Manganotti P. Corticospinal excitability in human subjects during nonrapid eye movement sleep: single and paired-pulse transcranial magnetic stimulation study. Exp Brain Res 2008.
[39] Rossini PM, Desiato MT, Lavaroni F, Caramia MD. Brain excitability and electroencephalographic activation: non-invasive evaluation in healthy humans via transcranial magnetic stimulation. Brain Res 1991;567(1):111–9.
[40] Fuggetta G, Fiaschi A, Manganotti P. Modulation of cortical oscillatory activities induced by varying single-pulse transcranial magnetic stimulation intensity over the left primary motor area: a combined EEG and TMS study. Neuroimage 2005;27(4):896–908.
[41] Brignani D, Manganotti P, Rossini PM, Miniussi C. Modulation of cortical oscillatory activity during transcranial magnetic stimulation. Hum Brain Mapp 2007.
[42] Romei V, Brodbeck V, Michel C, Amedi A, Pascual-Leone A, Thut G. Spontaneous fluctuations in posterior α-band eeg activity reflect variability in excitability of human visual areas. Cereb Cortex 2007.
[43] Romei V, Rihs T, Brodbeck V, Thut G. Resting electroencephalogram alpha-power over posterior sites indexes baseline visual cortex excitability. Neuroreport 2008;19(2):203–8.
[44] Thut G, Theoret H, Pfennig A, Ives J, Kampmann F, Northoff G, et al. Differential effects of low-frequency rTMS at the occipital pole on visual-induced alpha desynchronization and visual-evoked potentials. Neuroimage 2003;18(2):334–47.
[45] Komssi S, Savolainen P, Heiskala J, Kahkonen S. Excitation threshold of the motor cortex estimated with transcranial magnetic stimulation electroencephalography. Neuroreport 2007;18(1):13–6.
[46] Hung J, Driver J, Walsh V. Visual selection and posterior parietal cortex: effects of repetitive transcranial magnetic stimulation on partial report analyzed by Bundesen's theory of visual attention. J Neurosci 2005;25(42):9602–12.
[47] Silvanto J, Muggleton NG, Cowey A, Walsh V. Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation. Eur J Neurosci 2007;25(6):1874–81.
[48] Hilgetag CC, Theoret H, Pascual-Leone A. Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. Nat Neurosci 2001;4(9):953–7.
[49] Pascual-Marqui RD, Michel CM, Lehmann D. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 1994;18(1):49–65.
[50] Scherg M. Fundamentals of dipole source potential analysis. In: Gandori F, Hoke M, Romani GL, editors. Auditory evoked magnetic fields and potentials: advances in audiology. Basel: Karger; 1990. p. 40–70.
[51] Grosbras MH, Paus T. Transcranial magnetic stimulation of the human frontal eye field facilitates visual awareness. Eur J Neurosci 2003;18(11):3121–6.
[52] Posner MI, Petersen SE. The attention sytem of the human brain. Annu Rev Neurosci 1990;13:25–42.
[53] Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci 1995;18:193–222.
[54] Moore T, Fallah M. Microstimulation of the frontal eye field and its effects on covert spatial attention. J Neurophysiol 2004;91(1):152–62.
[55] Moore T, Armstrong KM. Selective gating of visual signals by microstimulation of frontal cortex. Nature 2003;421(6921):370–3.