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].

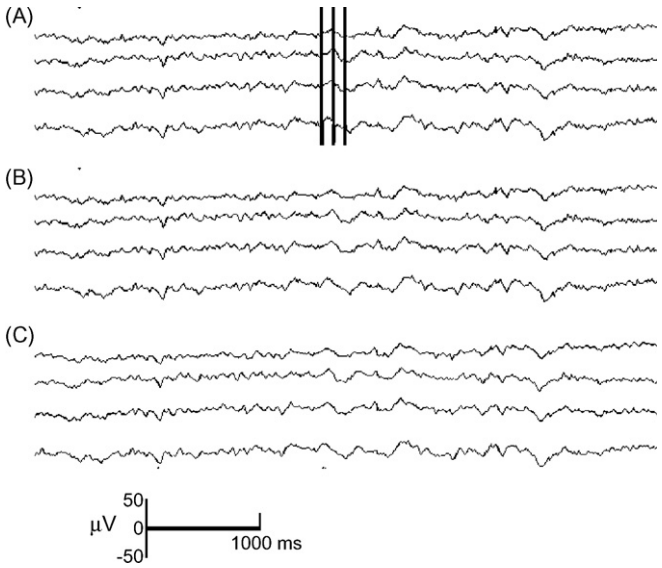

Fig. 1. (A) Raw EEG data from four occipital electrodes showing the TMS artifact when three pulses at 10 Hz are applied to the right frontal eye field; (B) the same dataset after artifacts are removed and data are extrapolated for the 40 ms time-window after each pulse; (C) after artifact removal the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