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Effects of theta burst stimulation protocols on phosphene threshold

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Abstract

Objective: We investigated the effects on occipital cortex, of two newly developed methods of repetitive transcranial magnetic stimulation (rTMS): continuous and intermittent theta burst stimulation (cTBS and iTBS), that lead to long lasting changes in excitability when applied over primary motor cortex.

Methods: Phosphene threshold to a single TMS pulse was measured before and after application of either continuous or intermittent theta burst stimulation (cTBS/iTBS; 600 total pulses at 80% phosphene threshold).

Results: In our cohort, cTBS increased phosphene threshold by an average of 10%. In contrast, iTBS, which transiently increases motor cortex excitability, had no effect on phosphene threshold.

Conclusions: cTBS can be applied successfully to non-motor areas of cortex, but iTBS may need modification to produce maximal effects.

Significance: cTBS maybe a new useful tool in disorders characterized by an abnormal state of activity of the visual cortex.

Keywords: Repetitive transcranial magnetic stimulation; Visual cortex; Phosphene threshold; Theta burst stimulation

1. Introduction

Since its introduction as a non-invasive method for stimulating the brain through the scalp (Barker et al., 1985), TMS has been widely used to study the physiology of the motor system. Stimulation over the motor cortex produces a twitch in contralateral muscles, whose amplitude and latency can give an objective measure of the activation of the cortico-spinal pathway. Single pulse stimulation most other areas of cortex produces no overt effects. An exception is the primary visual cortex where TMS pulses can induce the perception of flashes of light (phosphenes) in the absence of visual stimulation. Two possible explanations were put forward for these phenomena: TMS pulses could activate thalamocortical axons in the optic radiation with consequent excitation of cortical circuits in visual cortex (Amassian et al., 1998; Coway and Walsh, 2000; Marg and Rudiak, 1994) or, alternatively, TMS pulses could stimulate back-projecting fibres arising from extrastriate areas and targeting neurones in the primary visual cortex (necessary condition for phosphenes percept to be evoked) (Kammer et al., 2001; Pascual-Leone and Walsh, 2001).

In recent years, several studies on the visual cortex, in healthy subjects and in patients, have used the intensity threshold at which phosphenes are elicited (phosphene threshold, PT) as a specific and reliable index of visual cortex excitability in healthy subjects and in patients, similarly to MEPs amplitude, for cortico-spinal pathways (Afra et al., 1998; Antal et al., 2004; Aurora et al., 1998;

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Boroojerdi et al., 2002; Gerwig et al., 2003; Gothe et al., 2002; Mulleners et al., 2001; Stewart et al., 2001; Young et al., 2004). It has also been reported that it is possible to modulate the excitability of the visual cortex, as indexed by PT, through the application of repetitive TMS (rTMS) (Boroojerdi et al., 2000a; Brighina et al., 2002). The direction of the resultant excitability changes is the same way as it has been observed in the primary motor cortex (M1), i.e. low frequency rTMS increases PT in the same way as it reduces motor cortex excitability as assessed by reduction in MEP amplitude (Chen et al., 1997). Moreover, the modulatory effects of rTMS protocols depend on the functional state of the stimulated cortex (Boroojerdi et al., 2000b; Brighina et al., 2002; Fierro et al., 2005; Ziemann et al., 1998a,b).

Recently, two new rTMS protocols have been introduced: continuous and intermittent theta burst stimulation (cTBS and iTBS). They have their theoretical origins in the theta burst protocol often used to induce long term potentiation/depression (LTP/LTD) of synaptic transmission in brain slices (Hess et al., 1996), and they have been adapted to the TMS technique. These two protocols have been shown to suppress or enhance excitability of different M1 circuits for several minutes, and to induce changes in behavioural measures of reaction times (Huang et al., 2005). Although the basis of the after-effects of cTBS/iTBS is not completely understood, it has been suggested that it could involve LTP and LTD-like effects at cortical synapses.

The present study was designed to test whether cTBS and iTBS have effects on excitability of visual cortex similar to those observed in M1. Single magnetic pulses were delivered to the visual cortex of healthy volunteers to establish their PT before and after cTBS or iTBS were applied.

2. Materials and methods

2.1. Subjects

Eighteen right-handed healthy subjects (11 men and 7 women), aged between 20 and 35, were enrolled in this study. Because there are no safety guidelines on TBS protocols delivered with TMS, we asked our subjects an informed consent from the subjects and approval from the local ethics committee were obtained. Subjects were blindfolded with their eyes closed, whilst seated in a comfortable chair. They were advised that they may or may not perceive some visual 'phenomena' immediately after delivery of a single TMS pulse, and instructed to tell the experimenters if that was the case, either verbally or using a response device.

2.2. TMS protocol

TMS was administered using a magstim rapid magnetic stimulator (Magstim LTD, Whitland, Camarthenshire, UK), connected to a circular coil of 12 cm outer diameter (OD). This type of coil, held tangential to the scalp with the handle pointing upwards and the B-face towards the experimenter, has been reported to be the most effective in inducing phosphenes (Amassian et al., 1998; Kammer et al., 2001; Meyer et al., 1991). In this way, the second phase of the magnetic pulse induces a current in the brain with a latero-medial direction underneath the lower rim of the coil.

For accurate positioning of the coil, 4 points (2 cm apart) were identified on the INION–NASION line (I–N), starting from the INION and heading anteriorly, then 4 more points on the left and 4 on the right, in lines 2 cm from and parallel to the I–N line. The coil was first positioned on the midline with the lower rim just above the inion and then moved anteriorly and laterally across these points to determine the best place on the scalp to elicit phosphenes ('hot spot').

If phosphene perception was reported by the subject, a description of features—such as location (left or right, upper or lower hemifield, central or peripheral site), the colour if any, and whether it was static or moving—was requested. Throughout the investigation, one experimenter held the coil on the hot-spot position, which was also marked on the scalp, and another one controlled the variations in stimulator intensity.

2.3. Phosphene threshold determination

For each subject, the 'approximate PT' was determined as the approximate intensity at which a static phosphene was reported in both or in the left hemifield. This procedure had 3 main purposes: to select subjects that could reliably perceive phosphenes, to define the approximate PT and to determine the best position on the scalp to induce phosphenes in every subject (hot-spot).

We started with an initial intensity of 60% of the maximum stimulator output (MSO), increasing by 5% steps either until a phosphene was reported or until we reached 90% of MSO. At each intensity level, 10 consecutive pulses were delivered, and the approx PT was defined as the intensity giving rise to 5 out of 10 positive verbal reports. Subjects who gave equivocal answers (i.e. perceived phosphenes in the ipsilateral (right) hemifield, or was 'not quite sure of having seen something', or seemed unreliable for some other reason like drowsiness or loss of attention, etc.) were not studied further.

After having defined the hot-spot and the approximate PT, the PT estimate was refined by delivering, in random order, 10 pulses at intensities ranging from 80 to 120% of the approximate PT, with increments of 2% MSO.

In this session of the experiment, PT was evaluated by using a dedicated device (connected to a PC, equipped with