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Ten Years of Theta Burst Stimulation in Humans: Established Knowledge, Unknowns and Prospects

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ABSTRACT

Background/objectives: Over the last ten years, an increasing number of authors have used the theta burst stimulation (TBS) protocol to investigate long-term potentiation (LTP) and long-term depression (LTD)-like plasticity non-invasively in the primary motor cortex (M1) in healthy humans and in patients with various types of movement disorders. We here provide a comprehensive review of the LTP/LTD-like plasticity induced by TBS in the human M1.
Methods: A workgroup of researchers expert in this research field review and discuss critically ten years of experimental evidence from TBS studies in humans and in animal models. The review also includes the discussion of studies assessing responses to TBS in patients with movement disorders.
Main findings/discussion: We discuss experimental studies applying TBS over the M1 or in other cortical regions functionally connected to M1 in healthy subjects and in patients with various types of movement disorders. We also review experimental evidence coming from TBS studies in animals. Finally, we clarify the status of TBS as a possible new non-invasive therapy aimed at improving symptoms in various neurological disorders.

Abbreviations: AMT, active motor threshold; BA, Brodmann area; BCM, Bienenstock–Cooper–Munroe; BDNF, Brain Derived Neurotrophic Factor; CAR, cortisol awakening response; CB, calbindin; Cer, cerebellum; CD, cervical dystonia; COMT, catechol-O-methyltransferase; CBS, corticobasal syndrome; DA, Dark Agouti; DLPFC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; EEG, electroencephalography; GABA, γ-aminobutyric acid; GAD, glutamate decarboxylase; GTS, Gilles de la Tourette syndrome; HD, Huntington's disease; HFO, high frequency oscillation; $InsP_3Rs$, Inositol 1,4,5-trisphoshate receptors; LE, Long-Evans; LIDs, L-Dopa-induced dyskinesias; LTP, long-term potentiation; LTD, long-term depression; M1, primary motor cortex; MEP, motor evoked potential; MO, maximal machine output; MSA, Multiple System Atrophy; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; PAS, paired associative stimulation; PD, Parkinson's disease; PMd, dorsal premotor cortex; PSP, Progressive Supranuclear Palsy; PV, parvalbumin; RMT, resting motor threshold; rTMS, repetitive TMS; SD, Sprague–Dawley; SEP, somatosensory evoked potential; SMA, supplementary motor area; SNP, single nucleotide polymorphism; STP, short-term potentiation; TBS, theta burst stimulation; cTBS, continuous theta burst stimulation; iTBS, intermittent theta burst stimulation; TDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; TRP, transient receptor potential.

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Introduction

Until the late 1980s transcranial magnetic stimulation (TMS) machines could only deliver 1 stimulus every 4 s or so. However a repetitive stimulator was eventually produced that allowed repeated stimulation of the brain at high frequencies. Initially, repetitive TMS (rTMS) was used in "lesion" mode, to interrupt the function of language areas and thereby determine language dominance, or in "activation" mode to locate epileptic foci [1,2]. However, it was not long before groups began to investigate its potential for inducing after-effects that outlasted the period of stimulation, and which appeared to involve plastic changes in the excitability of cortical synapses. Theta burst stimulation (TBS) is one of many forms of rTMS that were developed after this pioneering work when more advanced stimulators were available [3]. Although it was first thought that TBS produced more powerful and reproducible effects than other rTMS methods, a claim that unfortunately has not stood the test of time, its main attraction is the speed of application. It takes 2–3 min or less to apply TBS protocols, making them more acceptable to participants than longer lasting protocols such as 1 Hz rTMS which can take 20–30 min; the same advantage means that it can even be used in unanaesthetized animals. This has led to a large body of literature, which we have tried to survey below. The review mainly focuses on experimental studies performed on the primary motor cortex (M1) or in other cortical regions known to be functionally connected to M1 in healthy subjects and in patients with various types of movement disorders. We also discuss the experimental evidence coming from TBS studies in animals. Finally, we evaluate the status of TBS as a possible new non-invasive therapy aimed at improving symptoms in various types of neurological disorders.

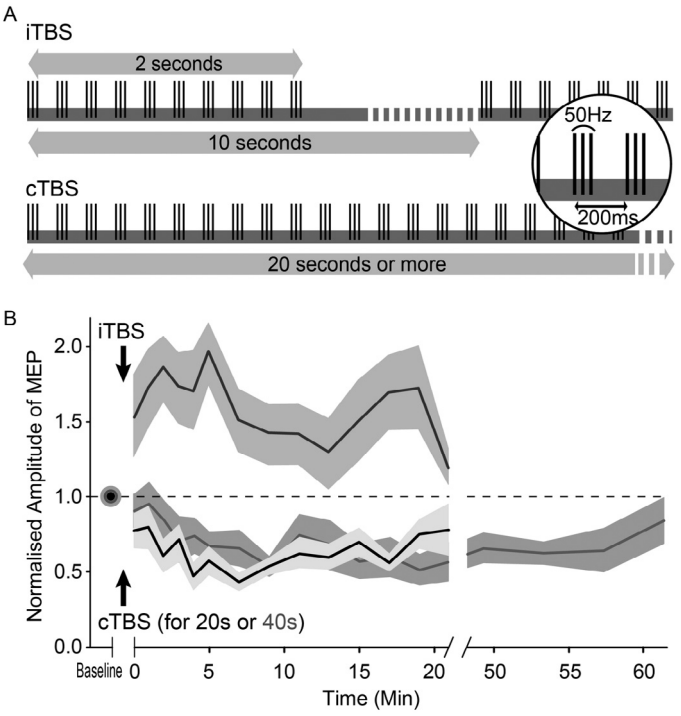

Figure 1. The patterns and effects of TBS. (A) The basic element of TBS is a 3-pulse burst at 50 Hz given every 200 ms (i.e. 5 Hz). Two major patterns, including iTBS and cTBS, are commonly used. A short train of 10 bursts lasting for 2 s is given every 10 s for 20 cycles in iTBS, while 100 or 200 continuous bursts are given continuously for 20 or 40 s, respectively, in cTBS. (B) iTBS produces a potentiation effect for around 20 min. In contrast, after AMT measurement cTBS for 20 and 40 s produces a depressive effect for 20 min and 60 min, respectively.

TBS in human studies

Neurophysiology of TBS

The original concept of TBS comes from the burst discharge at 4–7 Hz (the theta range in electroencephalography – EEG terminology) recorded from the hippocampus of rats during exploratory behaviour [4]. Theta burst patterns of stimulation are commonly used to induce plasticity in animal brain slices [5–7], and it seemed reasonable to adapt these to the human brain using TMS. The parameters were adjusted to match the capabilities of rTMS machines available at the time. Each burst had three pulses at 50 Hz, instead of the four pulses at 100 Hz typically used for stimulating brain slices. Bursts were given at 5 Hz, which is identical to that used in the animal preparation.

The first TBS protocol applied to human subjects was continuous TBS (cTBS) in which TBS was given continuously for 20 s [3]. It was initially surprising that cTBS reduced the amplitude of the motor evoked potentials (MEPs) for some 20 min since TBS in animal preparations typically enhanced synaptic efficacy resulting in long-term potentiation (LTP) rather than long-term depression (LTD). However, it has been noted that a longer train of stimulation may eventually lead to LTD if the stimulation period is long enough [8–10]. The TBS protocol was then adjusted to deliver repeated short trains mimicking what those commonly used for LTP induction in the animal studies. Such intermittent TBS (iTBS) successfully facilitated MEPs [3]. The most commonly used varieties of cTBS and iTBS are illustrated in Fig. 1A. iTBS enhances cortical excitability for 20 minutes or so whereas cTBS with either 300 or 600 total pulses (20 s or 40 s duration) leads to inhibition for 20 or 60 min respectively (Fig. 1B).

A single TMS pulse to the motor cortex evokes activity in corticospinal fibres that can be recorded directly in conscious humans through electrodes implanted into the epidural space at the high cervical level for the relief of pain [11]. Such recordings have shown that TMS evokes a series of descending waves of corticospinal activity [11]. The earliest wave is termed the D-wave because it is caused by direct activation of the axon of corticospinal neurons in the subcortical white matter. The later waves are called I-waves because they are due to synaptic activation of the same corticospinal neurons and they are numbered in order of appearance (I1, I2 etc) [11–13] (Fig. 2).

Epidural recordings before and after TBS show that cTBS and iTBS have differential effects on the I-wave components of the corticospinal volley. The cTBS protocol suppresses the I1 wave, whilst later I waves and the D-wave are much less affected (Fig. 2) [11,14]. Interestingly, the after effects of cTBS differ from those observed with other stimulation paradigms that suppress MEPs such as low-frequency (1 Hz) repetitive magnetic stimulation and paired associative stimulation with an interstimulus interval of 10 ms (PAS_{10}). These selectively suppress late I waves with no change in the amplitude of the I1 wave [11].

In contrast to cTBS, the iTBS protocol enhances late I-waves with no change in the amplitude of the I1 wave [15]. This suggests that iTBS affects a different population of neurons whose inputs to the corticospinal cells produce the late I-waves (Fig. 2). The effect of iTBS might be due to enhancement of synaptic transmission in the late I-wave circuit and/or to increased synchronization in the bursting inputs to corticospinal cells. This second effect is supported by the findings obtained in a single patient with chronic stroke who had epidural electrodes implanted in the epidural space of the upper spinal cord for treatment of pain. The I-waves recorded after iTBS of lower limb M1 were not only enhanced in amplitude but also much more synchronized [16] (Fig. 2). The reasons for the differ-