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Prolonged Continuous Theta-burst Stimulation is More Analgesic Than 'Classical' High Frequency Repetitive Transcranial Magnetic Stimulation

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) at high frequency (>5 Hz) induces analgesic effects, probably by activating pain modulation systems. A new rTMS paradigm – theta burst stimulation (TBS) – consists of bursts of three pulses at 50 Hz repeated five times per second. Like high frequency rTMS, both intermittent and prolonged continuous TBS (iTBS and pcTBS) lead to a facilitation of cortical excitability.
Objectives: (1) to evaluate the analgesic effects of neuronavigated iTBS and pcTBS, comparing them with those of classical high frequency rTMS (10 Hz) over the left M1, (2) to elucidate the role of conditioned pain modulation (CPM) in the antinociceptive effect of rTMS and (3) to investigate possible correlations between analgesia and cortical excitability.
Methods: Fourteen healthy volunteers participated in four experimental sessions, carried out in a random order (iTBS, pcTBS, 10 Hz rTMS or sham). Cold pain threshold, CPM and cortical excitability measurements were carried out before and after rTMS.
Results: We found that the analgesic effects of 10 Hz rTMS and pcTBS were significantly superior to those of sham rTMS. Moreover, pcTBS was significantly more effective than 10 Hz rTMS ($P = 0.026$). Analgesia did not seem to be driven by changes in CPM or cortical excitability.
Conclusion: Prolonged cTBS has considerable clinical potential, as it has a shorter treatment duration (by a factor 8) and stronger analgesic effects than the classical high frequency protocol. Studies in patients are required to confirm the potential of this new stimulation paradigm for clinical applications.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a safe, non invasive technique for cerebral cortex stimulation [1], the clinical applications of which have expanded considerably in recent years. Over the last decade, it has repeatedly been shown that rTMS of the primary motor cortex (M1) at high frequency (>5 Hz) induces analgesic effects against both experimental pain [2–7] and various chronic pain conditions [8–15].

The mechanisms underlying rTMS-induced analgesia remain unclear, but they probably involve pain modulatory systems [16], including the endogenous opioids systems [2] (for review, see [17]). These mechanisms are probably also dependent on changes in cortical excitability induced by the magnetic field, because the analgesic effects of rTMS in patients with chronic pain have been shown to be directly correlated with changes in intracortical modulation (i.e. short intracortical inhibition and intracortical facilitation) [12–14,18].

New rTMS paradigms involving theta burst stimulation (TBS) have recently been described [19]. TBS consists of bursts of three pulses at 50 Hz, repeated five times per second, mimicking the

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protocols used to induce long-term potentiation of synapses in experimental research [20]. Such stimulation sessions, which are much shorter than classical high frequency rTMS sessions, are thought to have stronger and more reproducible effects on cortical excitability. Intermittent TBS (iTBS) with 600 pulses induces a facilitation of cortical excitability [19,21]. By contrast, the effects of continuous TBS (cTBS) on cortical excitability seem to depend on the number of pulses. Inhibitory effects have been reported with 600 pulses [19,22,23] and facilitatory effects with 1200 pulses [21].

We therefore hypothesized that iTBS and/or prolonged cTBS (pcTBS) would yield analgesic effects similar to or, possibly, even stronger than those produced by 'classical' rTMS. We carried out a sham-controlled, randomized, double-blind, crossover study in healthy volunteers, to compare the analgesic effects of three rTMS protocols inducing motor cortex facilitation: classical high-frequency rTMS (10 Hz), 600 pulse iTBS and 1200 pulse pcTBS. Stimulation was applied to the left primary motor cortex and was neuronavigated, to improve the reproducibility of the stimulation.

We investigated and compared the potential mechanisms of action of these stimulation paradigms further, by systematically assessing cortical excitability and intracortical modulation before and after each stimulation. As rTMS-induced analgesia may be dependent on changes in pain modulatory systems [16,24], we also analyzed the effects of the stimulation on conditioned pain modulation (CPM). More specifically, we compared the effects of the three rTMS paradigms on the inhibition of a test experimental stimulus induced by heterotopic noxious stimuli, to assess possible changes in diffuse noxious inhibitory controls (DNIC) [25,26].

Materials and methods

This study was conducted at Ambroise Paré Hospital (Boulogne Billancourt, France) from December 2012 to July 2013. The protocol was approved by the appropriate local ethics committee. Paid healthy volunteers with no relevant clinical history, with a normal clinical examination and not on medication at the time of testing or during the previous month were included. All were right-handed non-smokers. The volunteers were carefully briefed about the experimental procedures of this study, which aimed to evaluate the efficacy of new rTMS protocols and to investigate the mechanisms of action underlying rTMS-induced analgesia. All participants gave written informed consent for participation.

Study design

The protocol involved four experimental sessions, held at least two weeks apart, in which we compared the effects of prolonged continuous TBS (pcTBS), intermittent TBS (iTBS), classical 10 Hz rTMS and sham stimulation on cold experimental pain. The order of these sessions for each volunteer was determined according to a randomized, double-blind design. In each session, the stimulation administered targeted the left primary motor cortex (Fig. 1).

Experimental procedures

Each volunteer underwent brain MRI (1.5 T, 3D T1-weighted axial) before the four stimulation sessions to rule out brain abnormalities and to facilitate the neuronavigation procedure.

During the sessions, subjects were seated in a comfortable reclining chair and asked to remain as relaxed as possible. Thermal perception was evaluated with quantitative sensory tests (QSTs) carried out in a quiet room at constant temperature (24–25 °C). We chose to assess the cold pain threshold (CPT) as it has been shown to be the most affected by rTMS-induced analgesia in healthy volunteers [5]. We assessed the CPTs with a Somedic thermotest (Somedic AB, Stockholm, Sweden). A contact thermode of Peltier elements measuring 25 × 50 mm was applied to the skin over both thenar eminences and over the left foot. The baseline temperature of the thermode was 32 °C. Cold pain thresholds (CPT) were determined for each of the three skin areas (both hands and the left foot), as the mean of three successive determinations, as previously described [2,5]. Once all the thresholds had been determined, suprathreshold stimulus (heat threshold +3 °C) was applied for 2 s on the right thenar eminence. After the stimulus, the volunteers were asked to rate pain intensity on a 10-cm visual analog scale (VAS) extending from 0 (no pain) to 100 (worst possible pain). Volunteers were informed that they could stop the stimulus at any time.

Conditioned pain modulation (CPM) was explored with a heterotopic painful cold conditioning stimulus and a painful heat test stimulus, to assess diffuse noxious inhibitory controls (DNIC) more specifically. The conditioning stimulus consisted of immersion of the left foot in cold water (between 4 and 8 °C) for 1 min. The test stimulus was applied to the right thenar eminence, in the form of suprathreshold heat stimulation, as described above (heat threshold +3 °C), with the left foot kept in the cold water. After the heat stimulus, the volunteers were asked to rate pain intensity on a VAS. The magnitude of the inhibition was noted as a percentage decrease in VAS score when the suprathreshold heat stimulus was applied alone rather than during immersion of the foot in cold water.

Transcranial magnetic stimulation

Magnetic stimulation was applied with a MagPro×100 machine (Magventure Tonika Elektronic, Denmark), using a cool-B65 figure-of-eight-shaped coil oriented tangentially to the scalp, in the anterior-posterior direction. This coil was fixed to an arm that could be adjusted in three dimensions. Sham stimulation was performed with a sham coil of identical size, color and shape, emitting a sound similar to that emitted by the active coil. The coil was positioned over the left M1 with an optical neuronavigation device (SyneikaOne, Syneika, France). Neuronavigation ensures perfect reproducibility between sessions and is more precise than the "standard" procedure of coil positioning [27].

The volunteers were fitted with ear plugs during rTMS. The resting motor threshold (RMT) was defined as the lowest intensity eliciting a motor evoked potential (MEP) with a peak to peak amplitude of at least 50 μV in 50% of trials. MEPs were recorded for the first interosseous muscle of the right hand, with an EMG amplifier module (Magventure Tonika Elektronic, Denmark) and surface electrodes (Alpine Biom, Denmark).

Repetitive TMS was applied at 80% of the RMT, as in previous studies in which that was sufficient to induce cold pain analgesia in healthy volunteers [2,5,28]. Three active and one sham stimulation were applied in a random order, with only one type of stimulation applied per session (Fig. 1C). Prolonged cTBS consisted of three pulses at 50 Hz (i.e. 60 ms) repeated 400 times at intervals of 200 ms (total of 1200 pulses in 1 min and 44 s). Intermittent TBS consisted of 20 trains (3 pulses at 50 Hz repeated 10 times at 200 ms intervals) with an intertrain interval of 8 s (total of 600 pulses in 3 min and 20 s). The 10 Hz rTMS procedure consisted of 15 trains of 10 s with an intertrain interval of 50 s (total of 1500 pulses in 14 min and 10 s). Among the 14 volunteers, 5 were randomly assigned to sham 10 Hz rTMS, 5 to sham pcTBS and 4 to sham iTBS. Pain threshold, cortical excitability or CPM variations were similar in these different subgroups and the results were pooled.

Short intracortical inhibition (SICI) and intracortical facilitation (ICF) were investigated with paired pulses, with the intensity of the conditioning stimulus set at 80% of the RMT and the intensity of the