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Original Article

Differential analgesic effects of high-frequency or accelerated intermittent theta burst stimulation of M1 on experimental tonic pain: Correlations with cortical activity changes assessed by TMS-EEG

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ABSTRACT

Accelerated intermittent theta burst stimulation (AiTBS) has attracted much attention in the past few years as a new form of brain stimulation paradigm. However, it is unclear the relative efficacy of AiTBS on cortical excitability compared to conventional high-frequency rTMS. Using concurrent TMS and electroencephalogram (TMS-EEG), this study systematically compared the efficacy on cortical excitability and a typical clinical application (i.e. pain), between AiTBS with different intersession interval (ISIs) and 10-Hz rTMS. Participants received 10-Hz rTMS, AiTBS-15 (3 iTBS sessions with a 15-min ISI), AiTBS-50 (3 iTBS sessions with a 50-min ISI), or Sham stimulation over the primary motor cortex on four separate days. All four protocols included a total of 1800 pulses but with different session durations (10-Hz rTMS = 18, AiTBS-15 = 40, and AiTBS-50 = 110 min). AiTBS-50 and 10-Hz rTMS were more effective in pain reduction compared to AiTBS-15. Using single-pulse TMS-induced oscillation, our data revealed low gamma oscillation as a shared cortical excitability change across all three active rTMS protocols but demonstrated completely opposite directions. Changes in low gamma oscillation were further associated with changes in pain perception across the three active conditions. In contrast, a distinct pattern of TMS-evoked potentials (TEPs) was revealed, with 10-Hz rTMS decreasing inhibitory N100 amplitude and AiTBS-15 reducing excitatory P60 amplitude. These changes in TEPs were also covarying with low gamma power changes. Sham stimulation indicated no significant effect on either cortical excitability or pain perception. These results are relevant only for provoked experimental pain, without being predictive for chronic pain, and revealed a change in low gamma oscillation, particularly around the very particular frequency of 40 Hz, shared between AiTBS and high-frequency rTMS. Conversely, cortical excitability (balance between excitation and inhibition) assessed by TEP recording was modulated differently by AiTBS and high-frequency rTMS paradigms.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is able to induce neuroplastic changes and bears clinical implications for certain psychiatric and neurological disorders. The schedule of rTMS delivery can be accelerated by applying multiple sessions of intermittent theta burst stimulation (AiTBS) per day, with the purpose to increase treatment efficacy as well as reducing the duration of treatment courses [1]. AiTBS has received fast-growing attention in the last few years since the introduction of the Stanford Neuromodulation Therapy (SNT) [2,3]. Indeed, there is a clear antidepressant effect of delivering multiple iTBS sessions per day (AiTBS) over the left dorsolateral prefrontal cortex (L-DLPFC) [4–7].

In light of the promising outcomes, it is unclear the relative efficacy of AiTBS on neural plasticity compared to conventional high-frequency rTMS. In fact, intersession interval (ISI) could be critical in the generation of accumulative effects with AiTBS protocols [for reviews see 1, 8]. Duration around 15 and 50 min are the two most common intersession intervals in AiTBS protocols. A series of experimental studies indicated that repeated iTBS sessions with a 15-min interval may not be able to

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generate additive neuroplastic changes [8–11]. Similarly, a few clinical trials revealed that AiTBS with a 15-min ISI had similar antidepressant efficacy with standard 10-Hz rTMS but not a superior effect [4,7]. In contrast, long-term potentiation (LTP) was increased by multiple iTBS sessions spaced apart by 1 h or longer but not when shorter intervals were employed [11]. However, this early plastic evidence primarily comes from animal studies or human spinocortical assessment, with scarce evidence from human cortical excitability.

Concurrent TMS and electroencephalogram (TMS-EEG) is able to evaluate local and distributed cortical excitability [12–14]. TMS-evoked potentials (TEPs), a series of reproducible peaks including N45, P60, N100, and P180 [15,16], provide a direct read-out of cortical excitation and inhibition following rTMS [17]. Using this technique, our group provided the first line of evidence whereby 10-Hz rTMS modulated N100 amplitude that was closely associated with rTMS analgesia [18]. However, there is very limited evidence on AiTBS effects on cortical excitability, except that one recent study demonstrated a smaller N100 amplitude in treatment-resistant depression [19]. Moreover, single-pulse TMS-induced oscillation is able to evaluate cortical responses following rTMS intervention. Recent studies indicated that excitatory rTMS (iTBS or 10 Hz) increased theta and gamma band oscillation [13,18].

This study was designed to systematically compare the effects on cortical excitability between two common forms of AiTBS and conventional high-frequency rTMS. The primary motor cortex (M1) was targeted as it has long been established to modulate corticomotor excitability [20,21], and has Level A evidence in treating neuropathic pain [22,23]. Healthy participants received 10-Hz rTMS, AiTBS-15, AiTBS-50, or Sham stimulation on four separate days. This study compared the effects of these different rTMS protocols on pain intensity and cortical excitability without any a priori hypothesis on the induced effects. Findings from this study would translate to the clinical applications rTMS in pain management and other conditions.

Methods

Experimental design and procedure

This was a double-blind, crossover, and randomised study. Participants visited the laboratory four times (≥7 days intervals), receiving a single session of M1 rTMS (10-Hz, AiTBS-15, AiTBS-50) or Sham stimulation with the sequence being pseudo-randomised and counterbalanced. All four protocols included a total of 1800 pulses but with different session durations (10-Hz rTMS = 18 min, AiTBS-15 = 40 min, and AiTBS-50 = 110 min). Sham stimulation was only performed in a random selection of twelve participants as a control condition. This design was incorporated from previous TMS studies to save the experimental burden of participants [24]. Before and after rTMS, 105 single pulses were delivered to the M1 region to assess neuroplastic changes. Participants also underwent a capsaicin pain protocol before and after rTMS in each session. The primary outcome measures included TEPs and oscillations, and the secondary outcome was pain perception. In terms of blinding, XC performed sequence randomization, YW performed rTMS intervention and BT collected the outcome measures. Both the participants and outcome assessor were blinded to the group allocation.

Participants

An a priori sample size calculation was performed based on the size of N100, which was reliably modulated by 10-Hz TMS in our previous study and has the highest signal-to-noise ratio [18,25]. Sample size calculation (alpha = 0.05, beta = 0.8, mean = 0.41, SD = 0.77) indicated a minimum of 22 participants for the study to be sufficiently powered [18,26]. A group of thirty healthy, right-handed, TMS-eligible [27] adults were recruited to account for potential dropouts. Potential participants initiated the contact from posts in the Hangzhou Normal University or the Affiliated Hospital of Hangzhou Normal University. They were then screened for eligibility. Handedness was determined by self-reporting of the participants without using the well-established Edinburgh Handedness Inventory [28]. Exclusion criteria included a history or current diagnosis of psychiatric disorder, or use of psychoactive medication, as assessed by the Mini International Neuropsychiatric Interview (MINI) [29]. Two participants withdrew from this study as pain induction failed with a pain score less than 3. Data from 28 participants (age range: 21–66 years, mean ± SD: 29.23 ± 13.83, 18 females) were therefore analysed. All participants provided a written informed consent prior to participation. This study was approved by the ethics committee in the Affiliated Hospital of Hangzhou Normal University (2022-E2-HS-044) and was conducted in accordance with the Declaration of Helsinki.

Pain protocol and intensity

Capsaicin application is a widely used tonic pain protocol that has been demonstrated to evoke tonic heat pain [30–32]. In this study, capsaicin (Chattem Chemicals Inc. 0.1%) was applied over the inner side of right wrist in an area of 2 × 2 cm and wrapped with medical tape. Pain experience was measured using a 0–10 visual-analogic scale (VAS) (0: no pain, 1–3: mild pain, 4–6: moderate pain, 7–10: severe pain) in a duration of 40 min at an interval of 10 min. In the capsaicin pain protocol, pain perception started to ascend within 10 min and reached to a peak amplitude around 30–40 min [30–32]. Data on pain experience was therefore determined with the max pain intensity within 30–40 min after capsaicin application. It is worth noting that capsaicin-induced tonic pain peaked within 30–40 min and decreased significantly at 90 min [30,33]. A single capsaicin session was thus not able to induce consistent pain for the purpose of the current study, due to the apparent different durations of rTMS protocols (i.e. from 18 to 40 and 110 min). We thus adopted a Pre and Post capsaicin paradigm that was successfully used in recent studies [34,35]. Capsaicin was removed from the skin when a pain protocol was done and the skin area was treated with an ice cube to reduce pain sensations. In order to reduce carryover effects, there was an interval of more than 2 h between the two sessions of pain induction.

Repetitive transcranial magnetic stimulation

rTMS was delivered to the left M1 with an intensity of 90% resting motor threshold (RMT). This intensity was used to coincide with the SNT studies [2,3]. A 90% RMT is also recommended to generate consistent analgesia in expert reviews [36]. It is noted that iTBS protocols were also delivered at 80% of the active motor threshold (AMT) in previous studies [37,38]. The 10-Hz rTMS protocol included 36 trains of 5-s stimulation given at 10 Hz, with the inter-train interval being set to 25 s (1800 pulses). The two AiTBS protocols each included three standard iTBS sessions totaling 1800 pulses, but with inter-session-intervals of 15 min (AiTBS-15) or of 50 min (AiTBS-50). A standard iTBS session consists of a burst of 3 pulses given at 50 Hz repeated every 5 Hz, in which a 2-sec train of TBS repeated every 10-sec for a total of 192 s [38]. Sham stimulation was randomised to the three active protocols between participants (4 of each, totaling 12 participants), but with a 75-mm high plastic block to avoid the penetration of the magnetic field [39].

Resting motor threshold and TMS-EEG

Resting motor threshold (RMT), defined as the minimum intensity to induce motor-evoked potentials (MEPs) > 0.05 mV of the first dorsal interosseous (FDI) muscle in 5/10 trials, was measured before each session. Single pulses to the hand region of the left M1 (45° to the midline, handle pointing backward) at 4s ± 10% jitter intervals were sent by a figure-eight coil connected to a Magstim Rapid^2 system (Magstim Company Ltd, UK). It is noted that delivering single-pulse TMS over the same site with an interstimulus interval of more than 3 s does not alter corticomotor excitability [40,41]. RMT was determined with the EEG cap on for consistency as rTMS and single pulses were both delivered with the

EEG cap on. Coil position was measured relative to the nasion and inion to facilitate consistent re-positioning of the coil between sessions [14, 42–44].

Single pulses were delivered to the left M1, which was located based on the hotspot method. A semi-grid method was used in which the coil was adjusted approximately half centimetre in each attempt to locate the hotspot. 'Hotspot' refers to the scalp location triggering the highest peak-to-peak MEP amplitude in EMG recordings. The coil was positioned at 45° relative to the midline (handle pointing backward), with the intensity being set to 110% RMT (Che et al., 2019). A total of 105 single pulses were delivered in order to increase the signal-to-noise ratio in TMS-EEG recordings [14,45]. A masking noise was played through earplugs during TMS-EEG recordings [13], with the sound level adjusted such that each individual could barely hear single-pulse TMS at 110% RMT. Induced current flows from the front end towards the handle for this coil [36], which was suggested to be provided in the assessment of the motor system with single and pair pulse TMS [46].

EEG recordings during single-pulse TMS took place in a temperature-controlled, sound-attenuated, and electrically shielded room. Participants sat in a chair with their eyes opening and looking forward. A 64-channel EEG cap (Brain Products GmbH, Germany) was used to record continuous EEG with FCz and AFz as the reference and ground electrode respectively. EEG impedances were kept below 5 kΩ throughout the recordings.

TMS-EEG data were analysed using EEGLAB [47] and custom scripts running on MATLAB platform (R2017b, the MathWork, USA). TMS-EEG data were preprocessed as previously reported [14,42,48]. Data were epoched around the TMS pulses (−1000 to 2000 ms) and baseline corrected (−500 to 50 ms). The large magnetic pulses were removed and interpolated (−5 to 20 ms). Data were then downsampled to 1000 Hz and were visually inspected for bad channels and trials containing excessive muscle activities. In each session, epochs across pre- and post-stimulation were concatenated to avoid bias in component rejection of the independent component analysis [49]. A first round of FastICA was performed to remove large muscle artefacts and decay artefacts using the semi-automated component classification algorithm [12,48]. Data were then filtered using Butterworth filters (band-pass = 1–100 Hz; band-stop = 48–52 Hz), and epochs were manually inspected again. The second round of FastICA was performed to remove non-neural artefacts, such as eye blinks, eye movements, persistent muscle activity, and electrode noise. Interpolation was then applied for removed channels. Data were then re-referenced to the common average. Finally, data were segmented into initial blocks (pre- and post-stimulation) for each session. The final pulse numbers were (Mean ± SD): Pre_10-Hz: 67.11 ± 21.44; Post_10-Hz: 70.18 ± 16.31; Pre_AiTBS-15: 68.93 ± 16.48; Post_AiTBS-15: 64.96 ± 20.45; Pre_AiTBS-50: 69.82 ± 14.57; Post_AiTBS-50: 70.25 ± 19.46; Pre_Sham: 68.17 ± 14.47; Post_Sham: 68.42 ± 18.37.

Time-frequency analyses were performed using Hanning tapered "mtmconvol" method in FieldTrip toolbox [50]. Power was calculated in the range of 1–100 Hz in the time window of −50 to 500 ms and baseline corrected (−50 to 0 ms) for each trial before averaging trials in each condition for each subject.

Statistical analysis

For pain perception, percent change was initially calculated from Pre- to Post-stimulation and was then examined with repeated measures of one-way ANOVA (rTMS: 10-Hz, AiTBS-15, AiTBS-50) in SPSS (IBM Corp, Armonk, NY, version 22). Pairwise comparisons were conducted using a Bonferroni correction ($\alpha \leq 0.05$).

For TEPs, non-parametric cluster-based permutation statistics were performed at a global level. This method is able to control multiple comparisons across EEG channels and time [51]. Statistics were conducted on peaks of interest. Time windows for each peak were determined based on previous studies (N45 (30–45 ms), P60 (50–75 ms), N100 (75–110 ms) and P180 (160–220 ms)) [13,18,52,53] as well as on the waveforms of our data (Fig. 3a). Comparisons were made between Pre- and Post-stimulation for each stimulation condition using paired T-tests. An observed statistics value was considered in the cluster permutation if it was below the threshold of 0.05 in at least two of the neighbouring channels [50]. We performed 5000 iterations of trial randomization for generating the permutation distribution, controlling for multiple comparisons across space ($P < 0.025$; two-tailed test).

For time-frequency data, the same cluster-based permutation tests were performed in all channels. Comparisons were initially made between Pre- and Post-stimulation for each stimulation condition ('within-comparison'). Statistical analysis was performed in delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), low-beta (12–20 Hz), high-beta (20–30 Hz), low gamma (30–45 Hz), and high gamma (45–100 Hz). Due to the significant between-condition differences in pain, EEG oscillation comparisons between AiTBS-15 and the other two active conditions ('between-comparison') were then performed using the delta score of each condition (Δ = Post–Pre).

Pearson's correlation analyses were conducted to evaluate brain-behaviour relationships between changes in pain perception, changes in TEP amplitude, as well as changes in EEG power.

Supplementary analysis

Supplementary analysis was performed on the twelve participants with a Sham condition. Specifically, a repeated measures of one-way ANOVA with four levels (10-Hz, AiTBS-15, AiTBS-50, Sham) was initially conducted on pain perception. TEP data was then analysed on the Sham condition from Pre-to Post-stimulation.

Results

Effects of rTMS on pain ratings

One-way ANOVA revealed a significant condition effect ($F_{1.99,53.93} = 6.82$, $P = 0.002$, $\eta_p^2 = 0.20$), with pairwise comparisons indicating that both 10-Hz rTMS ($Mean_{10\text{-}Hz} = -6.48$, $Mean_{AiTBS\text{-}15} = 9.78$, $P_{Bonferroni} = 0.007$) and AiTBS-50 ($Mean_{AiTBS\text{-}50} = -4.26$, $Mean_{AiTBS\text{-}15} = 9.78$, $P_{Bonferroni} = 0.022$) reduced pain perception compared to AiTBS-15 (Fig. 2). There was no significant difference between 10-Hz rTMS and AiTBS-15.

Plastic effects of rTMS on TEPs

Time-domain signals were initially presented as butterfly plots as well as voltage distribution across the scalp with baseline data averaged from three conditions (Fig. 3). Single-pulse TMS over the left M1 resulted in a series of negative and positive peaks including N45, P60, N100 and P180, in line with previous TMS-EEG studies assessed in the motor cortex [54–57]. Each peak showed a distinct pattern in scalp topography, indicating the spreading of voltage distribution across time.

Cluster-based permutation tests revealed that the amplitude of the primary TEP component of interest, N100, was significantly decreased from Pre-to Post-10-Hz rTMS ($P_{corrected} = 0.025$) (Fig. 4a). Moreover, the topography of this change was mainly distributed around the left motor cortex where rTMS pulses were delivered (Fig. 4b).

In terms of AiTBS-15, cluster statistics indicated that the amplitude of P60 was reduced from Pre-to Post-stimulation ($P_{corrected} = 0.021$) (Fig. 4c). The topography of this effect was also distributed around the left central cortices (Fig. 4d). There were no significant changes in either peak of interest following AiTBS-50 (Fig. 4e and f).

Effects of rTMS on EEG oscillations

In the 10-Hz rTMS condition, cluster-based permutation statistics revealed a significant increase in low gamma power in the time window of 55 ms–85 ms from Pre-to Post-stimulation ($P_{corrected} = 0.015$). The

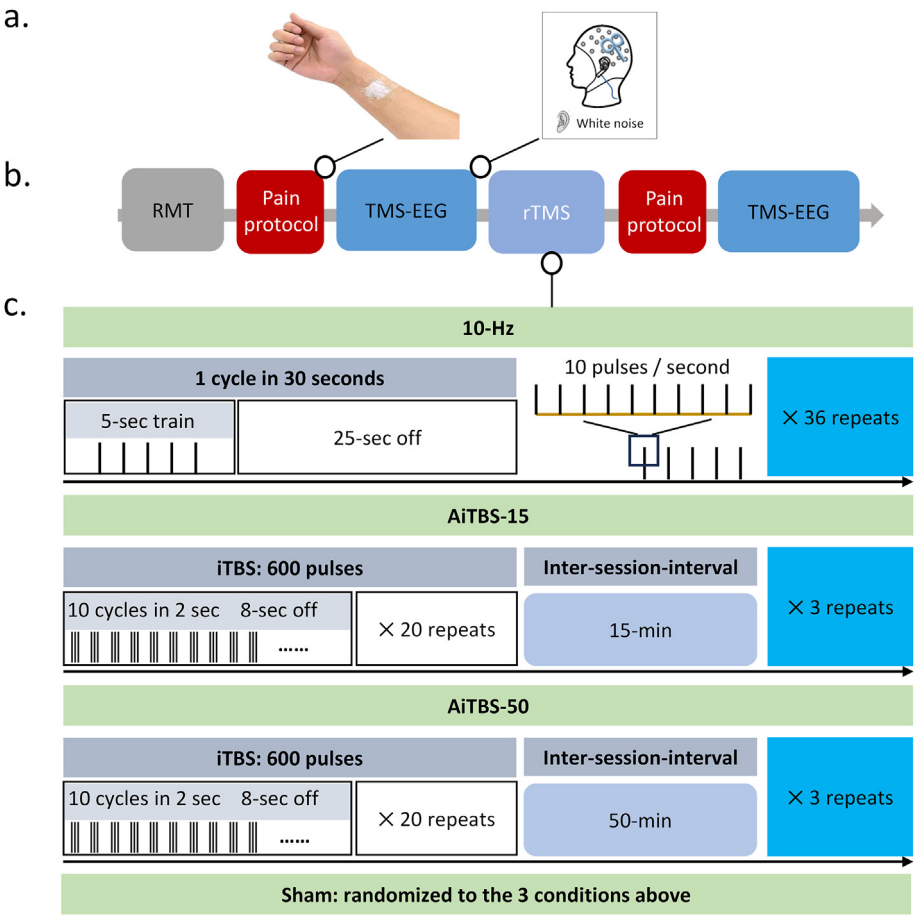

Fig. 1. Experimental procedure. Participants received 10-Hz rTMS, AiTBS-15 (ISI = 15 min), AiTBS-50 (ISI = 50 min), or Sham stimulation over the primary motor cortex on four separate days. Participants underwent a capsaicin pain protocol and TMS-EEG assessment before and after rTMS in each session.

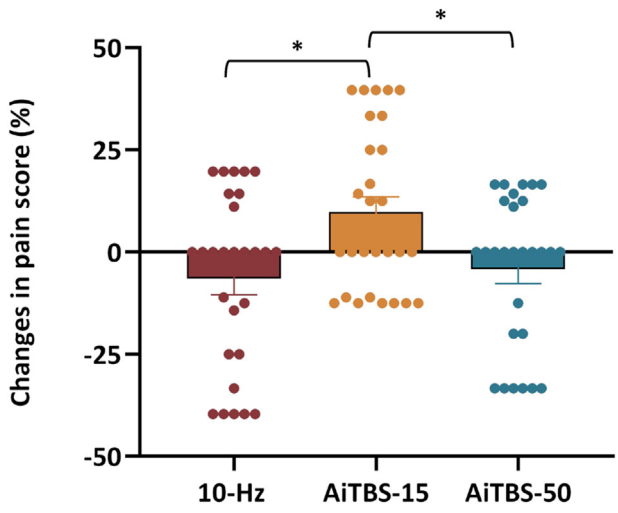

Fig. 2. Pain perception results. 10-Hz rTMS ($P_{Bonferroni}$ = 0.007) and AiTBS-50 ($P_{Bonferroni}$ = 0.022) reduced pain perception compared to AiTBS-15. * indicates $P_{corrected} < 0.05$.

topography of this power increase had a bilateral central distribution similar to the topography of the TEP cluster (Fig. 5a–c). No difference was found in any other frequency bands.

In the AiTBS-15 condition, two significant clusters were revealed by the cluster-based permutation statistics. The first cluster was decreased low gamma power in the time window of window of 82 ms–153 ms from Pre-to Post-stimulation ($P_{corrected}$ = 0.020) (Fig. 5d–f). This cluster distributed around the left central regions similar to the P60 TEP cluster. The second cluster was a decrease in theta power in the time window of window of 24 ms–155 ms ($P_{corrected}$ = 0.023), which also had a distribution mainly surrounding the left central regions (Fig. 5g and h). There was a significant positive correlation between decreased P60 amplitude and theta power (P = 0.013) (Fig. 5i).

In terms of the AiTBS-50 condition, no significant difference was found in any frequency bands in whole-brain analyses. A further local analysis revealed a significant increase in left frontocentral low gamma power in the time window of 135 ms–148 ms from Pre-to Post-stimulation ($P_{corrected}$ = 0.018) (Fig. 5j-l). It is noted that a local analysis was performed whereby a cluster was revealed by whole-brain statistics but did not survive whole-brain corrections.

Between-condition analysis using delta score also revealed increased low gamma power in the 10-Hz rTMS compared to the AiTBS-15 condition. This significant cluster was observed in the time window of 50 ms–95 ms ($P_{corrected}$ = 0.020), and distributed around the left central regions (Fig. 6a–c). In addition, AiTBS-50 resulted in increased low gamma power compared to the AiTBS-15 condition, with the cluster distributing around the left frontocentral cortices and in the time window of 128 ms–153 ms ($P_{corrected}$ = 0.011) (Fig. 6d–f).

Further correlation analysis indicated that changes in low gamma power induced by all three conditions (i.e. decrease and increase in low gamma power) were negatively associated with changes in pain perception (i.e. decrease and increase in pain) from Pre-to Post-stimulation (P = 0.008) (Fig. 6g). In addition, changes in low gamma power induced by 10-Hz rTMS (i.e. increased) and AiTBS-15 (i.e. decreased) were positively associated with changes in respective TEP amplitude (i.e.

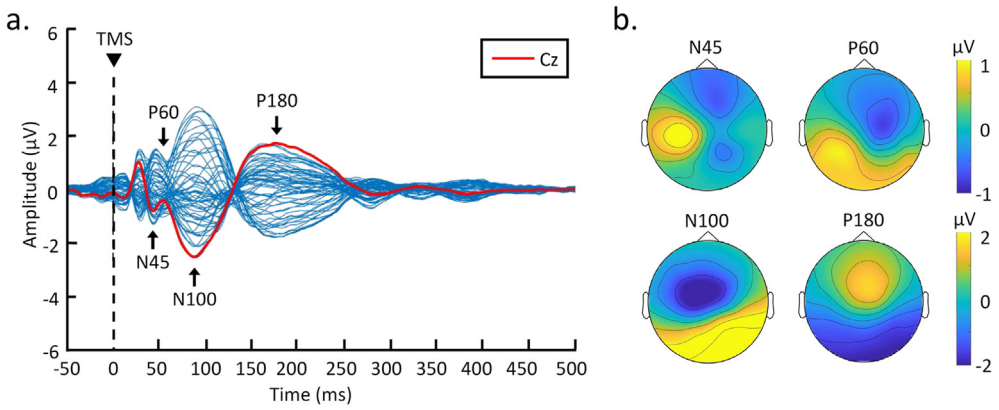

Fig. 3. Baseline TEP waveform and voltage distribution. a) Butterfly plots of all electrodes with peaks of interest are highlighted. The waveform in red line indicates Cz for illustration purposes. Data were combined across three active conditions. b) Topographical voltage distribution for the peaks of interest, indicating the spreading of voltage distribution across time.

N100 and P60 in each condition) from Pre-to Post-stimulation ($P = 0.006$) (Fig. 6h). AiTBS-50 did not induce significant TEP changes and was not introduced to this correlation.

Supplementary results

Pre to Post analysis indicated that Sham stimulation had no significant effect on pain perception, any TEPs or frequency data ($P_s > 0.05$) (see Supplementary Materials Fig. 1).

Between-condition analysis on change score (Post-Pre) revealed that Sham stimulation had no significant effect on pain ($P_{Bonferroni} > 0.05$) in the subgroup of 12 participants. We then extracted significant features from the TMS-EEG data and made comparisons between active and sham conditions. Results indicated that change scores of the significant features in TEP (i.e. N100, P60) were also significant in the comparisons of active and sham conditions (see Supplementary Materials Fig. 2). In addition, change scores of oscillations also revealed the same results as to the Pre-to-Post analysis, except that the low gamma change in AiTBS-15 and AiTBS-50 did not reach statistical significance due to a small sample of 12 but with a same pattern as to the main analyses (see Supplementary Materials Fig. 2). Overall, the Sham stimulation further confirmed the excitability changes in the active conditions.

Safety assessment

Two participants suffered a mild headache in the AiTBS conditions on the first visit. Another two individuals experienced a slight scalp discomfort each in the 10 Hz and AiTBS condition. However, all of these sensations disappeared within minutes. Overall, the protocols were safe and well-tolerated.

Discussion

Using concurrent TMS-EEG, this study systematically compared the effects of two common forms of AiTBS and 10-Hz rTMS on cortical excitability as well as analgesic efficacy [58,59]. AiTBS-50 and 10-Hz rTMS were more effective in pain reduction compared to AiTBS-15. Our data revealed low gamma oscillation as a shared excitability change across all three active rTMS protocols but demonstrated completely opposite directions. Moreover, changes in low gamma oscillation were associated with changes in pain perception across these three conditions. In contrast, three rTMS protocols induced distinct changes in TEPs, whereby 10-Hz rTMS decreased inhibitory N100 amplitude and AiTBS-15 reduced excitatory P60 amplitude. Sham stimulation revealed no significant effect on either cortical excitability or pain perception.

It is acknowledged that only twelve participants were randomised to receive sham stimulation. This was designed to reduce the testing burden for participants [24]. Our data indicated that sham stimulation had no significant effect on pain perception or cortical excitability. More importantly, our data indicated that 10-Hz rTMS and AiTBS-50 were equally effective in reducing pain perception compared to AiTBS-15 (Fig. 2). Previous studies have repetitively demonstrated an analgesic effect following 10-Hz rTMS [60–62]. Our data provided novel findings that AiTBS-50 was comparable with 10-Hz rTMS in analgesia. The excellent antidepressant efficacy induced by AiTBS-50 protocol incorporated many more iTBS sessions per day [2,3]. Meanwhile, it is striking to find that AiTBS-15 was more likely to increase pain experience in our data. This is compatible with the inhibition of cortical excitability as discussed in later sections.

Using TMS-EEG, we provided interesting findings that 10-Hz rTMS resulted in a smaller N100 amplitude in the left motor cortex where single pulses were applied. The N100 deflection is considered to be the most robust TMS-EEG component [63], which is associated with $GABA_B$-mediated postsynaptic inhibition [17,64,65]. Using inhibitory 1-Hz rTMS, studies demonstrated a larger N100 amplitude in the motor cortex (i.e. target), which suggested an increase in postsynaptic inhibition following inhibitory rTMS [66,67]. Similarly, our group found a smaller N100 amplitude following excitatory 10-Hz rTMS over the prefrontal cortex [68]. Therefore, decreased N100 amplitude in our data suggests a reduction in cortical inhibition induced by excitatory stimulation. More interestingly, N100 changes were accompanied by increased low gamma oscillation spreading over the bilateral motor cortex (Fig. 5a–c). An early increase in gamma oscillation (~50 ms) was consistently induced by single-pulse TMS over occipital, parietal, and frontal cortices [69]. Gamma oscillation reflects coordinated neuronal activity and is implicated in spike-timing dependent plasticity [70]. Together with a reduced N100 amplitude, these findings indicate reduced cortical inhibition and increased cortical excitability induced by 10-Hz rTMS.

In line with a trend to increase pain perception, our neurophysiological data revealed decreased cortical excitability following AiTBS-15. AiTBS-15 reduced the P60 amplitude surrounding the target region (Fig. 4c and d). A growing body of literature indicated this peak to reflect cortical excitability [71,72]. We further provided evidence that AiTBS-15 inhibited theta and low gamma oscillation in the left central and centroparietal regions (Fig. 5d–h). Theta oscillation following single pulses was found to be increased by excitatory iTBS and decreased by inhibitory cTBS respectively [13]. Moreover, our data revealed a significant correlation between decreased P60 amplitude and theta power (Fig. 5i), further confirming the inhibitory effects of AiTBS-15 on cortical excitability. Our data extend the literature by presenting an inhibitory influence of AiTBS-15 on both cortical excitability and pain perception.

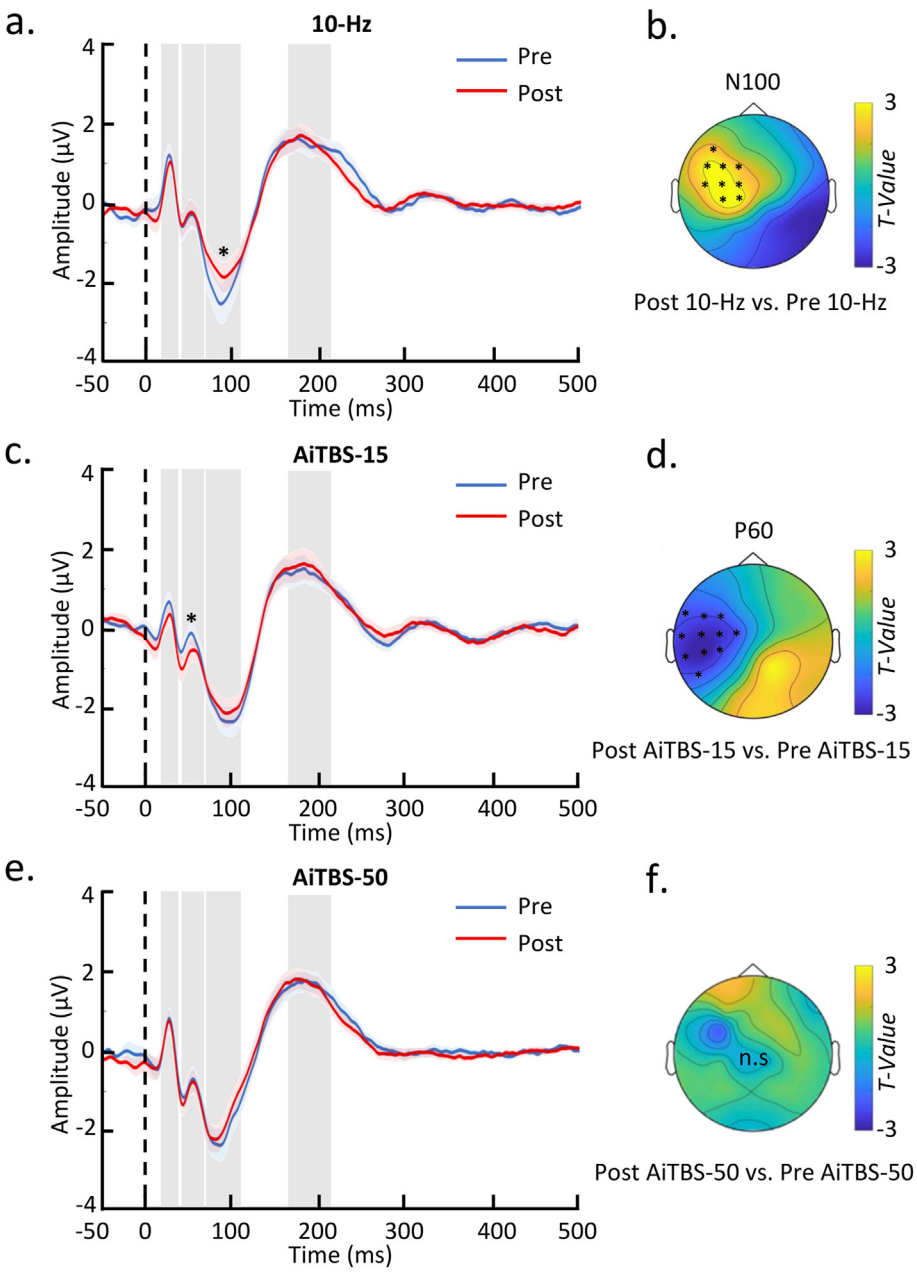

Fig. 4. TEP changes following stimulation. a-b) The amplitude of N100 was significantly decreased from Pre-to Post-10-Hz rTMS ($P_{corrected}$ = 0.025). The topography of this change was mainly distributed around the left motor cortex where rTMS pulses were delivered. c-d) AiTBS-15 decreased the amplitude of P60 from Pre-to Post-stimulation in the left central cortices ($P_{corrected}$ = 0.021). e-f) There were no significant changes in either peak of interest following AiTBS-50. n.s denotes non-significant.

Compared with 10-Hz or AiTBS-15, AiTBS-50 did not induce significant changes in TEPs from pre-to post-stimulation (Fig. 4e and f). However, frequency data revealed a significant increase in low gamma power in the left frontocentral regions (Fig. 6i–k). This finding suggests increased cortical excitability following AiTBS-50 that is shared by 10-Hz rTMS and inversely modulated by AiTBS-15. The literature has limited evidence on the neurophysiological mechanisms of AiTBS-50 apparently due to the novelty of this protocol. An animal study indicated that LTP was only increased by multiple iTBS sessions spaced apart by 1 h or longer [11]. This is consistent with the idea of 'spaced learning' whereby reinforcing trials or sessions should be spaced by long and/or irregular intervals to achieve optimal efficacy [73]. In human study, a pioneering study revealed that two iTBS sessions with a 54-min interval reduced N100 amplitude in a course of 30 treatments in treatment-resistant depression (TRD) [19]. However, this effect was not specific to AiTBS-50 but was also evident in continuous AiTBS with no interval. Building on these studies, we provided novel mechanistic data demonstrating increased low gamma oscillation as evidence of cortical excitability in AiTBS-50.

Given the opposite effects on pain and oscillation, we further compared EEG change scores between these three rTMS protocols. Both 10-Hz rTMS and AiTBS-50 increased low gamma power compared to AiTBS-15 (Fig. 6a–f). More importantly, low gamma oscillation was entrained to opposite directions by different rTMS protocols, and when combined together, changes in low gamma power were negatively associated with pain perception following stimulation (Fig. 6g). It is noted that gamma oscillation overlaps with muscle activity [74–76]. This oscillatory activity is also associated with facial muscle tone [77,78]. Our results were identified around a relatively narrow band around 40 Hz (30–45 Hz), which may not fully represent the whole gamma range (30–100 Hz). Beyond this, low gamma oscillation surrounding 40 Hz is closely involved in specific thalamocortical oscillations, such as sensory activation [79–82]and pain experiences [83]. Our findings therefore demonstrate a critical role of ~40 Hz gamma oscillation in the context of sensory/nociceptive neuromodulation.

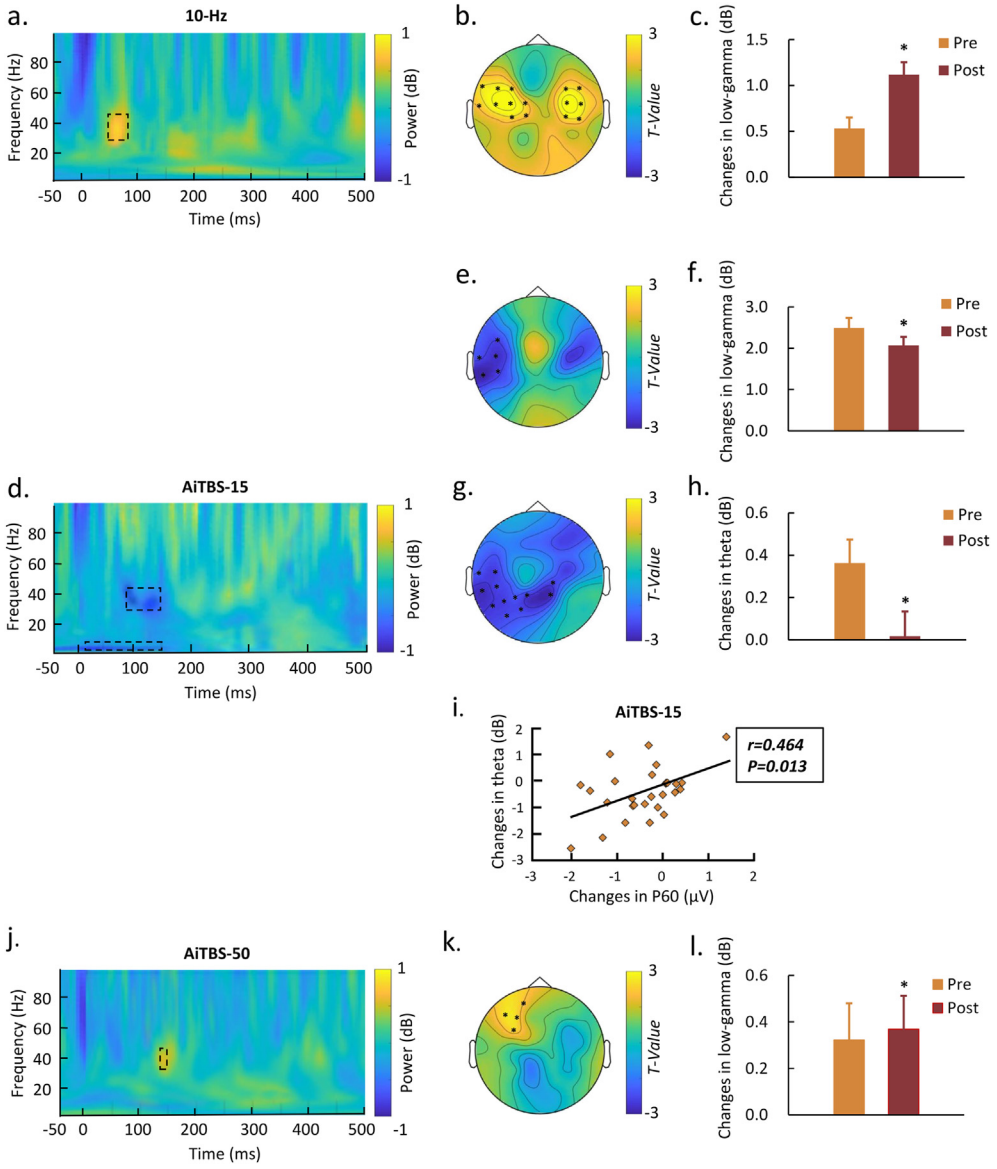

Fig. 5. Single-pulse TMS-induced oscillations from Pre-to Post-stimulation. a-c) 10-Hz rTMS increased lower gamma power in the bilateral motor cortices ($P_{corrected}$ = 0.015). d-f) AiTBS-15 decreased low gamma power around the left central regions ($P_{corrected}$ = 0.020). d,g,h) AiTBS-15 also decreased theta power in the left central regions ($P_{corrected}$ = 0.023). i) There was a significant positive correlation between decreased P60 amplitude and theta power post AiTBS-15 (P = 0.013). j-l) AiTBS-50 also increased lower gamma power in the left frontocentral regions ($P_{corrected}$ = 0.018).

To date, iTBS has been predominantly investigated to accelerate the schedule of rTMS delivery. It is worth noting that cTBS is also able to reduce experimental-induced pain [84,85] and depression symptoms [86,87]. It remains to be established whether accelerated cTBS could be used to improve rTMS efficacy and efficiency. Moreover, our findings highlight the importance of pain models in rTMS studies. We applied capsaicin to model neuropathic pain in this study. Other studies have induced sustained muscle soreness and mechanical hyperalgesia to better model other chronic pain conditions such as musculoskeletal pain [88, 89]. These data together highlight the importance of nociceptive fibres (e.g. A δ and C fibres) that can be selectively targeted by different pain protocols and their application to model different chronic pain conditions [90]. In addition, it is important to distinguish rTMS-induced excitability changes at the cortical (e.g. TEPs, oscillations) and corticospinal levels (e.g. MEP, motor volume). Overall, future studies are warranted to develop more efficient stimulation paradigms, along with a more integrated assessment of excitability changes, and more accurate experimental models of certain chronic conditions.

There were some limitations in this study. The main limitation of this study is the fact that it was an acute modulation of experimental pain. There are clear differences in the patterns and mechanisms of analgesia produced by cortical stimulation between provoked pain in healthy subjects and in patients with chronic pain [91,92]. Our results thus lack of a predictive value for what might be obtained in the context of chronic pain treatment. We designed a broad age range with the intention of increasing the generalisability of our findings. However, it is noted that age could impact the neurophysiological properties measured by concurrent TMS-EEG as well as on rTMS effects [93–96]. Future studies may wish to clarify age effects in AiTBS and 10-Hz paradigms. Our results were generated from a group of healthy participants that may not directly translate to chronic pain patients. Chronic pain conditions demonstrate alterations in cortical excitability [97], future studies may wish to validate these findings in chronic pain conditions. Frequency-domain results in the AiTBS-50 condition were revealed with local analyses. Although these results were consistent across time and condition comparisons, future studies need to be performed with larger sample and/or more iTBS sessions. Changes in pain perception were small following stimulation as pain perception is relatively stable in healthy controls. It is expected to see increased analgesia in chronic pain patients induced by rTMS treatments [60]. Although hotspot methodology is accurate in identifying the motor cortex with the assistance of EMG response, it is not as accurate as MRI-guided neuronavigation which was not feasible in the present study

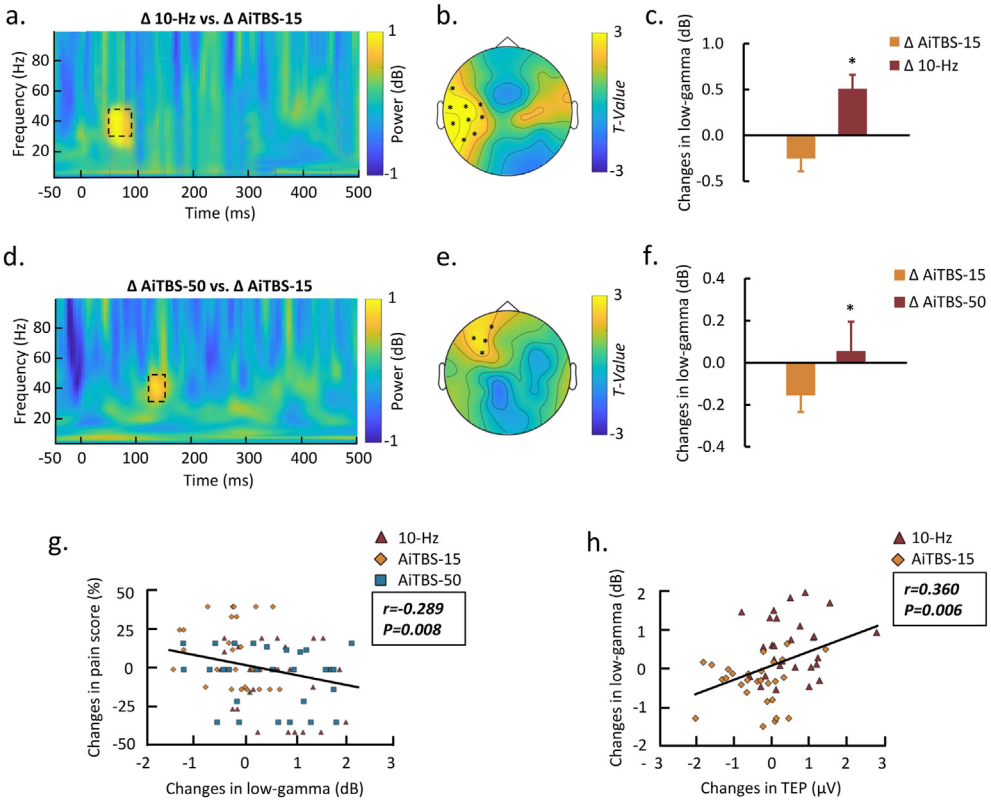

Fig. 6. Between-condition comparisons of single-pulse TMS-induced oscillations. a-c) There was an increased low gamma power in the 10-Hz rTMS compared to the AiTBS-15 condition in the left central regions ($P_{corrected}$ = 0.020). d-f) AiTBS-50 resulted in increased low gamma power compared to the AiTBS-15 condition in the left fronto-central regions ($P_{corrected}$ = 0.011). g) Changes in low gamma power induced by all three conditions were negatively associated with changes in pain perception from Pre-to Post-stimulation (P = 0.008). h) Changes in low gamma power induced by 10-Hz rTMS (i.e. increased) and AiTBS-15 (i.e. decreased) were positively associated with changes in respective TEP amplitude (i.e. N100 and P60 in each condition) from Pre-to Post-stimulation (P = 0.006).

[98]. We used a multiple capsaicin paradigm to induce consistent tonic pain for the purposes of the current study. A single capsaicin paradigm could also be considered given a limited duration of study designs.

In conclusion, AiTBS-50 and 10-Hz rTMS are equally effective in pain reduction compared to AiTBS-15. Low gamma oscillation is a shared cortical excitability change across these rTMS protocols but in opposite directions depending on the stimulation protocol.

Contributors

BT, XC contributed to study design, data collection, data analysis, and writing-up. JC contributed to study design, data collection, and writing-up. YL, QL, YW, SS and YY contributed to data collection.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Data Availability

All the data and codes generating findings of this work are available upon the request from the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurot.2024.e00451.

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