The effect of pulse shape in theta-burst stimulation: monophasic vs biphasic TBS

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Prior presentation

Abstracts on the early stages of this work were presented as posters at the Neuroscience 2022 meeting and the 5th International Brain Stimulation Conference.

Conflict of interest and Financial disclosures

TD, MMS and KW have pending patent applications for TMS device circuits and control algorithms. TD and KW have received grant funding (including an MRC iCASE studentship) and materials for research from Magstim Ltd. MMS is currently employed by Magstim Ltd. JOS, CJS and MF have no conflicts of interest.

Highlights

- Mono- and biphasic theta burst stimulation were applied with modulation-based TMS
- Effects on corticospinal excitability were assessed using motor evoked potentials
- Monophasic intermittent TBS increased MEP amplitude more than biphasic

Abstract

Background

Intermittent theta-burst stimulation (iTBS) is a transcranial magnetic stimulation (TMS) protocol which can temporarily modulate the corticospinal excitability. Conventionally, TBS is only applied using biphasic pulses due to hardware limitations. However, monophasic pulses are hypothesised to more selectively recruit cortical neurons than biphasic pulses which may improve the effect of iTBS. A custom-made pulse-width modulation-based TMS device with improved energy recovery and pulse-shaping capabilities allows the generation of monophasic iTBS.

Objective

To compare the effects of monophasic and biphasic iTBS on motor corticospinal excitability in healthy volunteers.

Methods

Thirty volunteers participated in three separate sessions, where monophasic and biphasic iTBS were applied to the primary motor cortex (active condition) or the vertex (control condition) using a custom-made TMS device. Changes in corticospinal excitability were quantified using the peak-to-peak amplitude of motor evoked potentials (MEP) with single-pulse TMS collected at baseline and at 5 - 60 minutes after the application of TBS.

Results

Both monophasic and biphasic active iTBS led to significant increases in MEP amplitude compared to baseline, with monophasic iTBS showing significantly larger effects (linear mixed effect model analysis: ($\chi^2(1) = 8.48$, $p = 0.004$)), even after subtracting the control condition from the active conditions ($\chi^2(1) = 6.21$, $p = 0.013$).

Conclusions

This study demonstrates that the pulse shape affects the extent to which TBS can modulate corticospinal excitability. Monophasic intermittent TBS has the potential to increase the efficacy of clinical treatment protocols in the future.

Key words: Transcranial magnetic stimulation, Theta burst stimulation, Pulse-width modulation, Pulse shape, Plasticity

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive tool for neuroscientific research and is increasingly used for diagnosis and therapy in clinical practice [1]. It uses the fundamental principles of magnetic induction to modulate the nervous system: A brief electric current is applied to a stimulation coil, creating a changing magnetic field, which can induce a voltage in the brain tissue underneath. When applied repeatedly, TMS can increase or decrease the corticospinal excitability of the targeted area even beyond the stimulation duration [2].

Different stimulation waveforms have been shown to recruit different neural populations, have different excitation thresholds and different effects on corticospinal excitability [3-8]. However, the stimulation pulses and patterns generated by conventional TMS devices are limited by the device hardware and usually confined to either monophasic or biphasic damped cosine pulses, where the exact shape and length of the pulse is determined by the resonance between the device components [9]. For monophasic pulses, the current flow is commonly stopped half-way through the cycle and the energy is dissipated through a resistor. This restricts not only the choice of pulse waveforms and widths but also the achievable repetition rates [10]. One example for this is a repetitive TMS protocol called theta burst stimulation (TBS), where bursts of 3 pulses are applied at 50 Hz and repeated every 200 ms [11]. TBS is currently only applied using biphasic pulse shapes since large amounts of energy need to be recovered after each stimulation pulse to sustain the repetition rates which conventional devices can mostly only achieve with biphasic stimulation pulses. Intermittent (i) TBS, where TBS is applied continuously for 2s followed by an 8s break and then repeated, is used in the treatment of major depressive disorder (MDD), where it is applied daily to the dorsolateral prefrontal cortex over several weeks [12] but moderate response rates leave the need to optimise the protocol.

Monophasic pulses are thought to more selectively recruit cortical neurons and have been shown to more strongly modulate cortical excitability than biphasic pulses when used in rTMS protocols [1, 6, 8, 13]. In another patterned TMS protocol, quadripulse stimulation (QPS), bursts of four pulses are applied at inter-stimulus intervals of 1.5-1250 ms, repeated every 5s over 30 min [14]. A study comparing the after-effects of monophasic and biphasic QPS found that monophasic QPS induced stronger and longer lasting after-effects compared with biphasic QPS [15]. These findings lead to the hypothesis that applying TBS with monophasic pulses may be more effective than biphasic TBS.

Recent technological developments of TMS devices using switching circuits rather than the conventional resonance circuits have allowed more control over the TMS parameters and better energy recovery from the stimulation pulses [9, 16-18]. The programmable (p)TMS, a TMS device developed within our research group, which uses pulse-width modulation (PWM) to control cascaded inverters, enables more control over the pulse shapes by approximating a reference pulse of arbitrary shape using discrete voltage levels [9]. Previous computational modelling and an in-human study indicated that the generated approximations of conventional pulse shapes with this method have similar effects on the motor cortex of healthy volunteers as the pulses generated by a conventional TMS device [19, 20]. Additionally, the device is able to effectively recover energy after each pulse, allowing the generation of monophasic TBS.

In this study, we use this custom-made pulse-width modulation-based TMS device to generate monophasic and biphasic TBS and compare the effects on the corticospinal excitability of healthy volunteers.

Materials and Methods

Ethical approval

This study and the use of the pTMS device in this study were approved by the local ethics committee at the University of Oxford (Central University Research Ethics Committee, R75180/RE008). All participants gave their written informed consent prior to participating.

Participants

30 healthy volunteers (16 females, aged 19-33 years, mean age 24.5 years) participated in three data collection sessions for this single-blind, within-participants crossover study. All participants were right-handed as assessed by the Edinburgh Handedness Inventory [21], reported no current significant medical condition or any other contraindication to TMS.

Transcranial magnetic stimulation

Single-pulse monophasic TMS was applied using a Magstim 200 stimulator (Magstim Co., UK) and all TBS protocols were applied using the pTMS stimulator. The pulse waveforms generated by the pTMS stimulator were designed to closely approximate the conventional biphasic and monophasic pulses generated by a Magstim Rapid^2 and a Magstim 200, respectively. The same 70 mm figure-of-8 coil (Magstim Co., P/N 9925–00) was connected to both stimulators during stimulation blocks if the resting motor threshold (RMT) was sufficiently low to avoid coil overheating during the TBS protocol (below 44% of the maximum stimulator output (MSO) of the Magstim 200). For higher thresholds, a separate 70 mm figure-of-8 coil was used for each stimulator (N = 3). Individuals with RMTs above 47% MSO of the Magstim 200 in the familiarisation session were excluded from the study to ensure the pTMS stimulator could generate all iTBS sequences at 70% of the RMT (N = 3).

The participants were seated in a chair with their arms resting on a pillow on top of a table in front of them. The coil was placed over the first dorsal interosseous (FDI) hotspot of the left primary motor cortex, where the lowest pulse intensity elicited MEPs in the right FDI. The coil was held by the operator and oriented at 45º to the midline with the handle pointing posteriorly which results in a posterior-anterior current flow in the brain for the monophasic pulse. The current of the biphasic pulse was reversed in the software, such that the current direction of the dominant second phase of the pulse matched the current flow of the monophasic pulse [3, 5] while the coil handle was pointing posteriorly. A Brainsight neuronavigation system (Rogue Research Inc., Montreal, Canada) was used to track the position and orientation of the coil. Surface electromyography (EMG) of the right FDI was recorded using disposable neonatal ECG electrodes (Kendall, Cardinal Health, UK) in a belly-tendon montage with a ground electrode over the ulnar styloid process. EMG signals were sampled at 10 kHz, amplified with a gain of 1000, filtered (10 Hz - 1000 Hz) and recorded using a D440 Isolated Amplifier (Digitimer, Welwyn Garden City, UK), a Micro1401 (Cambridge Electronic Design, Cambridge, UK) and Signal software version 7.01 (Cambridge Electronic Design). The unwanted 50 Hz line noise was attenuated by subtracting a replica of the measured noise from the input signal using a HumBug Noise Eliminator (Digitimer).

The motor hotspot was determined and recorded using the Brainsight software and the RMT, defined as the minimum intensity required to evoke an MEP of ≥50 μV peak-to-peak amplitude in 5 out of 10 consecutive trials, was determined by applying 10 pulses at each intensity and inspecting the EMG traces visually in real time for each device. To find the RMT, the pulses were triggered automatically via scripts in Signal version 7.01 (Magstim device) and Control desk (pTMS2 device) software at inter-pulse of 5 seconds (± 15%).

Procedure

Each participant attended three separate data collection sessions at least one week apart, as well as a separate familiarisation session beforehand if the participant was naïve to TMS, where TMS was introduced to the participant and the hotspot and thresholds for the different parameters and devices were found. During each data collection session the timeline was as follows (Fig. 1): After confirmation of the hotspot and the motor threshold, two baseline blocks were recorded 5 minutes apart, iTBS was applied 10 minutes after the start of the first baseline block and follow-up blocks were recorded every 5-10 minutes for the following hour (at 5, 10, 15, 20, 30, 40, 50 and 60 min after the start of the TBS protocol). Both the baseline blocks and the follow-up blocks consisted of 30 pulses applied at 120% of the RMT at inter-pulse intervals of 5 seconds (± 15%) using the Magstim 200 stimulator which generates a monophasic pulse. The applied TBS protocol consisted of 600 either monophasic or biphasic pulses applied at 70% of the RMT [22] using the pTMS stimulator. For each participant, two sessions were active conditions, where TBS was applied to the motor hotspot, and one session was a control condition, where TBS was applied to the vertex (similar to [23]). About half of the participants (N=14) received monophasic pulses in the control condition, the other half received biphasic pulses. The coil was lifted from the participants' heads between each stimulation block and participants were instructed to keep their hands as relaxed as possible.

The three sessions were performed at the same time of day for each participant and the session order was randomised and counter balanced. The participants were blinded to the stimulation condition.

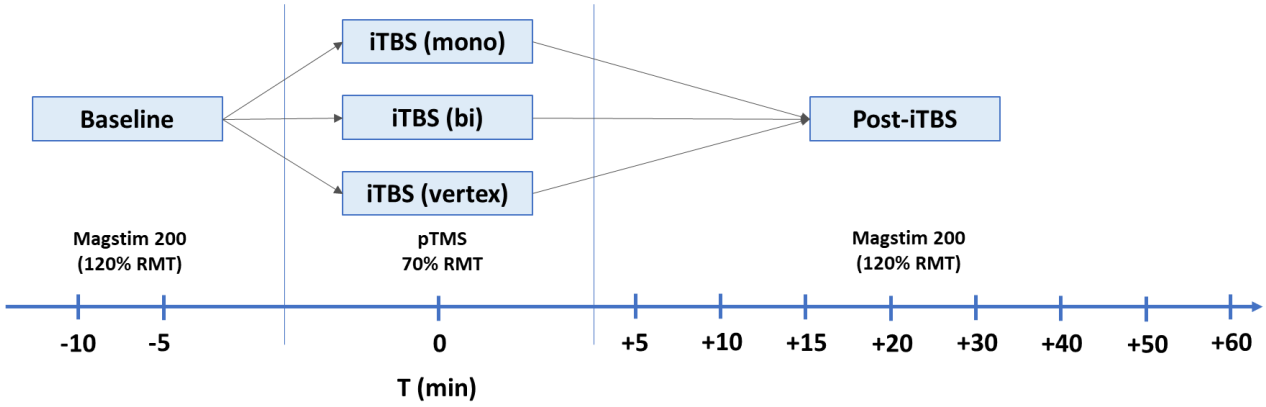

Fig. 1: Overview of study design representing the flow of data collection at each visit. Each participant received each TBS condition on separate days (at least one week apart) in counter balanced order. Baseline MEPs (30 pulses applied at 120% of the resting motor threshold) were collected in 2 separate blocks 10 and 5 min before the start of the TBS administration. iTBS was applied to the primary motor cortex (active condition) or the vertex (control condition) using monophasic or biphasic pulses for 190s. After TBS, MEPs were collected every 5 min for the first 20 min and then at 10-min intervals up to 60 min in the same way as the baseline.

Data processing

The data was processed in Python using a custom script. Since muscle activation can influence MEP amplitude, trials were excluded if the root mean square (RMS) of the EMG trace in the 90ms before the TMS stimulus (excluding the 5ms preceding the pulse) exceeded 0.02 mV or if the RMS was 0.005 mV larger than the RMS during the silent period after the MEP, to not unnecessarily exclude trials which included electrical artefacts which did not affect the measurement. The peak-to-peak MEP amplitude was calculated in the 15 – 60 ms time window after the TMS pulse was applied. Since the data of over 90% of the stimulation blocks was not normally distributed (Shapiro-Wilk < 0.05), the median (rather than the mean) of each time point was taken. The two baseline time points were averaged for each participant to give one

baseline value per session. For each participant within each condition, the change in MEP amplitude compared to the baseline was calculated by subtracting the baseline of each condition from each post-TBS time point, similar to McCalley et al [24]. Grand-average values for each condition were calculated by averaging over all post-TBS time points (5-60 mins). To control for the variability observed when taking MEP measurements across the one-hour time window, the MEP values of the control condition were subtracted from the MEP values of the active TBS conditions for all time points.

Data analysis

Repeated Measures analysis of variance (ANOVA) with factors time (baseline 1 and 2) and condition (monophasic, biphasic, control) was used to compare the peak-to-peak amplitude of the first and second baseline measurement and the baseline measurements across the conditions.

To investigate whether iTBS led to an overall increase in the amplitude of the MEPs, grand averages across all post-TBS time points were compared against zero using one-sample one-tailed t-tests for the active conditions (monophasic and biphasic TBS). A one-sample two-tailed t-test was used to assess the control condition. Pairwise t-tests were used to compare the grand averages across conditions and Bonferroni correction was used to correct for multiple comparisons for significant results. Effect sizes are reported using Cohen's d.

Linear mixed effects (LME) models were used to analyse the effect of the pulse shape on the change in MEP amplitude across time points in the active TBS conditions. This allowed the model to account for the amplitude of the MEPs at baseline for each condition by including it as a factor in the model, instead of accounting for the baseline by calculating a percentage change which commonly fails to accurately model physiological processes [25]. Participants were included as a random effect; baseline amplitude, time (5-60 min post-iTBS) and TBS

condition (monophasic, biphasic) were included as fixed effects in the LME models. The effect of including the TBS condition in the model was assessed by comparing it with a model without the TBS condition using likelihood ratio testing. The χ^2 statistics representing the difference in deviance between the successive models and the p values obtained using the Satterthwaite's method for denominator degrees-of-freedom and F-statistic are reported [26]. The analysis was repeated with the control-subtracted data. All linear mixed effects models were created and analysed using purpose-written R code using the LME4 package [27]. The significance level was set to 0.05 for all analyses.

Results

Resting motor threshold intensities did not differ between conditions at baseline ($F(2, 58) = 0.43$; $p = 0.65$) and a two-way Repeated Measures ANOVA revealed no significant differences either between the first and second baseline measurements within each session ($F(1, 29) = 1.27$; $p = 0.27$), nor between the TBS sessions ($F(2, 58) = 0.13$; $p = 0.88$).

Both active TBS conditions led to increased corticospinal excitability

Fig. 2 shows the grand average over the follow-up period (5-60 min post-TBS) after subtracting the baselines. Monophasic iTBS led to an increase in MEP amplitude of 0.30 mV (± 0.07mV SEM) compared to baseline and biphasic iTBS led to an increase of 0.19mV (± 0.05mV) which indicates a significant increase in corticospinal excitability in both conditions (monophasic: $t(29) = 4.60$; $p < 0.001$; $d = 0.84$; biphasic: $t(29) = 3.66$; $p < 0.001$; $d = 0.67$). iTBS over the vertex did not lead to a significant increase over the same time period (0.06mV (± 0.05mV), $t(29) = 1.29$; $p = 0.209$; $d = 0.23$). Pairwise t-tests showed that only the monophasic grand average was significantly larger than the control (monophasic vs control: $t(29) = 2.86$; $p = 0.023$ (Bonferroni corrected); $d = 0.75$; monophasic vs biphasic: $t(29) = 1.71$; $p = 0.098$; $d = 0.37$; biphasic vs control: $t(29) = 2.03$; $p = 0.052$; $d = 0.44$).

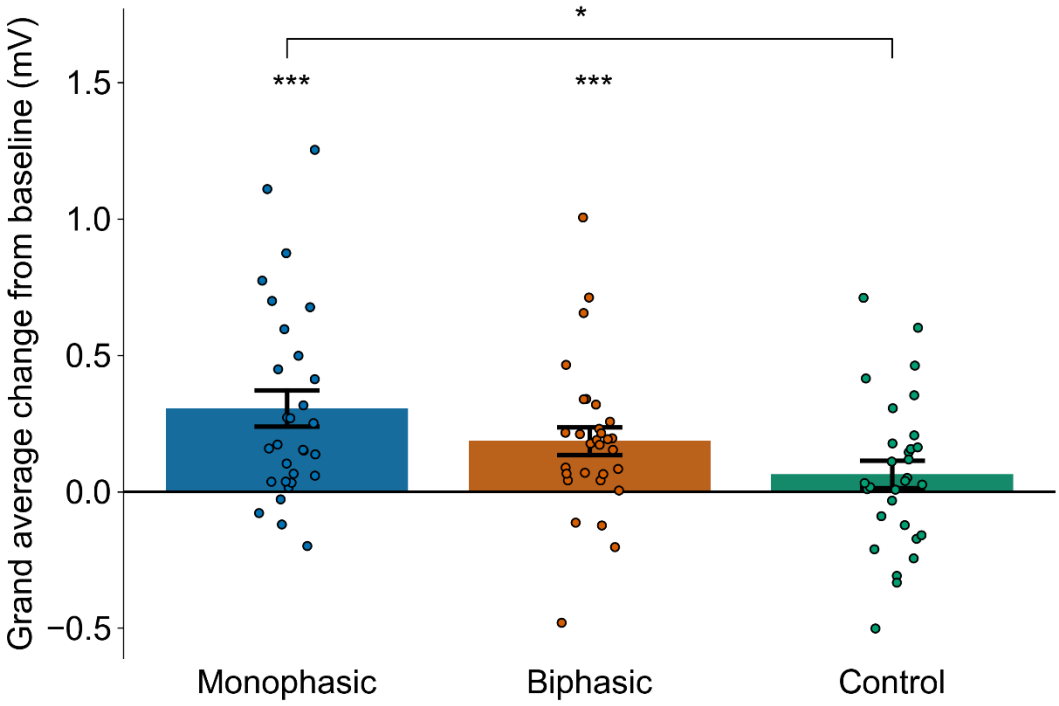

*Fig. 2: Average change in MEP amplitude compared to baseline across 60-min post-iTBS time period for the active (monophasic and biphasic) iTBS condition and the control condition. Individual participants are indicated by dots, the bars indicate group means and the error bars represent standard error of the mean. Asterisks indicate significance (***: $p < 0.001$; *: $p < 0.05$).*

Pulse shape affects iTBS effect

Fig. 3a shows the changes in MEP amplitude across the 60-minute follow-up period for each condition. Raw plots for each individual participant are shown in Fig. S1. Comparing the LME models with and without the fixed effect of TBS condition using likelihood ratio testing showed that the pulse shape during iTBS (monophasic, biphasic) had a significant effect on the change in MEP amplitude ($\chi^2(1) = 8.48$, $p = 0.004$) in the active conditions. Examination of the summary output for the model including the TBS condition indicated that the change in MEP amplitude was on average 0.12 mV higher in the monophasic relative to the biphasic TBS condition (B = 0.12, SE = 0.04, t = 2.93). Fig. 3b shows the model fit for both active conditions.

Similarly, after subtracting the MEP values of the control condition from the active conditions to control for the variability across the post-TBS time window (Fig. 3c), the likelihood ratio test still showed a significant effect of the pulse shape on the change in MEP amplitude ($\chi^2(1) = 6.21$, $p = 0.013$) with changes in MEP amplitude being on average 0.11 mV higher in the monophasic relative to the biphasic TBS condition ($B = 0.11$, $SE = 0.05$, $t = 2.50$).

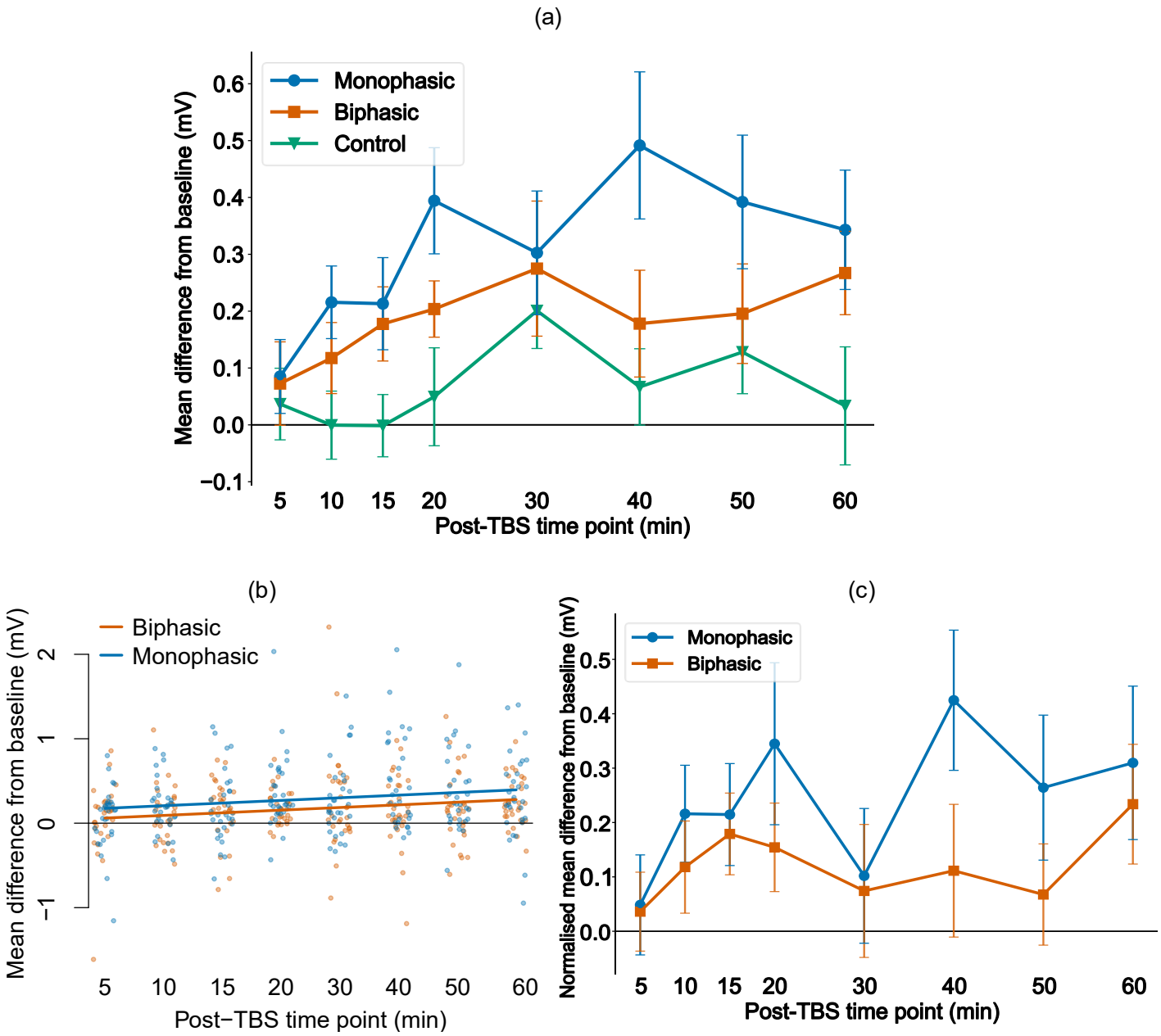

Fig. 3: Mean change in motor evoked potential amplitude (difference from baseline) over time for the different TBS conditions. (a) The mean change in MEP amplitude for the active monophasic and biphasic iTBS conditions and the control condition are shown across the post-TBS time points. (b) Visualisation of the fit of the linear mixed effect models to the data from the active (monophasic and biphasic) TBS conditions. Solid lines show the model prediction, single dots show partial residuals as generated using the 'visreg' function in R. (c) The group average for the active monophasic and biphasic TBS conditions normalised by the control

condition by subtracting the MEP values of the control condition from the MEP values of the active TBS conditions for all time points. Error bars indicate standard error of the mean.

Discussion

In this study, both monophasic and biphasic iTBS applied to the primary motor cortex increased corticospinal excitability as measured using MEPs. The application of iTBS using the pulse-width modulation based TMS device resulted in excitability increases as expected from studies applying iTBS using conventional resonance-based devices. On the group level, monophasic iTBS induced larger plasticity effects than conventional biphasic iTBS, confirming the importance of pulse shape in repetitive TMS protocols. TBS applied to the vertex in the control condition did not lead to significant MEP increases and the effect of pulse shape in the active conditions was sustained even when subtracting the control condition results from the active conditions.

Choice of probing pulses

To measure the changes in motor corticospinal excitability, single pulses were applied at 120% of the RMT similar to e.g. [28, 29]. Several previous studies, including the early TBS studies [30], use the intensity needed to elicit 1mV MEPs at baseline and during the follow-up period. However, as the maximal amplitude of the MEPs differs between participants, some participants may not be able to reach peak-to-peak amplitudes much higher than 1mV which can contribute to the high variability across participants [31]. Studies have suggested that plasticity effects may be best probed at a percentage of the resting motor threshold to take into account this difference in the input-output characteristics of the participants [32]. This reduces the risk of ceiling and flooring effects but increases the variability in the amplitude of the MEPs of baselines between participants. This was accounted for in the analysis of this study by including the baseline as a factor in the LME model.

Additionally, the shape of the single pulses was chosen to be monophasic and they were applied using a conventional Magstim 200 for all conditions. While this allowed the direct comparison of the effects across the TBS conditions, monophasic and biphasic pulses may activate different pathways during the applications of TBS. Using monophasic pulses therefore limits the ability to probe the potentially different pathway activated with biphasic pulses [13, 33]. Future research should investigate if the effects are different if biphasic pulses are used to measure the excitability changes.

Directionality of pulse currents

The direction of the current induced in the brain affects which neuron populations are activated and influences the size of the motor threshold [3, 5]. In this study, the monophasic pulses were applied to induce currents in the posterior-anterior direction both for single pulses and the TBS protocol, as this has been shown to have the lowest thresholds [5] and may therefore be the best current direction to increase the corticospinal excitability. The biphasic pulses were applied to match this current direction in the second phase of the pulse as this is thought to be the dominant activating phase of the biphasic pulse [5]. Future studies should evaluate and compare the effects of different current directions of the different pulse shapes both for the single pulses and the TBS protocol to determine the optimal current direction.

Intermittent TBS vs continuous TBS

Intermittent TBS is a protocol that tends to increase the excitability of the targeted area. In its counterpart, continuous (c)TBS, the 50Hz bursts are continuously repeated at 5Hz without the 8s break between burst trains which has been shown to decrease the excitability. While cTBS was not tested in this study, the effects of using monophasic pulses may translate to the cTBS protocol as well, as inhibitory protocols applying monophasic pulses at 1Hz have been shown to decrease the excitability more effectively than biphasic pulses [4, 8].

Further considerations to improve TBS

Monophasic pulses approximating the pulse shape of conventional stimulators were used in this study, but other pulse shapes or widths may cause larger effects in TBS and other repetitive TMS protocols. With the newer TMS devices such as the pTMS device used in this study, researchers gain the ability to investigate more parameters to optimise the effects of TBS. Other studies looking at the number of pulses per burst [34], different stimulation intervals [33, 35] as well as the total number of pulses [24, 36] show further possible avenues to increase the plasticity effects observed with the stimulation. While these are commonly tested in the motor cortex, any possible translation of the observed effects into clinical populations when stimulating areas such as the dorsolateral prefrontal cortex in the treatment of major depressive disorder need to be tested in clinical studies.

Vertex stimulation as control condition

In the control condition, iTBS was applied to the vertex of the head, using the same parameters as in the active conditions, to achieve a realistic control condition with similar skin sensation and audio effects [23, 37]. The purpose of the control condition was to control for the natural variability observed in MEP measurements when taken over the same time period as in the active conditions. However, as the brain was still stimulated in this condition albeit in a different location, network effects may influence the results.

Limitations

Due to the technical setup of the study, it was conducted in a single-blinded manner, where the participants were blinded to the condition and hypothesis but the experimenters were aware of the stimulation condition. This was partially due to the programming needed for the custom-made pTMS device to generate monophasic or biphasic pulses and the fact that the coil was placed in a different location during the control condition. Additionally, the experimenters

interacted with the participants during the 2-3h long sessions which may have an influence on the results and the MEP variability, though the use of a within-participants crossover design should help to mitigate this potential issue to some extent.

Conclusions

This study confirms that the pulse shape affects the group level plasticity effects observed after iTBS, with monophasic pulses leading to larger increases in MEP amplitude. This adds to the literature exploring improvements of the TBS protocol in the hope of enhancing plasticity induction protocols for other applications in basic neuroscience and medical practice such as depression therapy.

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Rights Retention

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Data availability statement

The data and relevant scripts will be made available on the Open Science Framework.

Authorship contributions

MMS and TD designed and built the pTMS device. MMS, KW and JO conceptualized and performed the study. CS and MF advised on study design and data analysis. KW performed the statistical analysis and drafted the manuscript. JO and TD provided funding for the study. All authors revised and approved the final version of the manuscript.

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