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Neuronal tuning: Selective targeting of neuronal populations via manipulation of pulse width and directionality

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ABSTRACT

Introduction: Motor evoked potentials (MEP) in response to anteroposterior transcranial (AP) magnetic stimulation (TMS) are sensitive to the TMS pulse shape. We are now able to isolate distinct pulse properties, such as pulse width and directionality and evaluate them individually. Different pulse shapes induce different effects, likely by stimulating different populations of neurons. This implies that not all neurons respond in the same manner to stimulation, possibly, because individual segments of neurons differ in their membrane properties.
Objectives: To investigate the effect of different pulse widths and directionalities of TMS on MEP latencies, motor thresholds and plastic aftereffects of rTMS.
Methods: Using a controllable pulse stimulator TMS (cTMS), we stimulated fifteen subjects with quasi-unidirectional TMS pulses of different pulse durations (40 μs, 80 μs and 120 μs) and determined thresholds and MEP AP latencies. We then compared the effects of 80 μs quasi-unidirectional pulses to those of 80 μs pulses with different pulse directionality characteristics (0.6 and 1.0 M ratios). We applied 900 pulses of the selected pulse shapes at 1 Hz.
Results: The aftereffects of 1 Hz rTMS depended on pulse shape and duration. 40 and 80 μs wide unidirectional pulses induced inhibition, 120 μs wide pulses caused excitation. Bidirectional pulses induced inhibition during the stimulation but had facilitatory aftereffects. Narrower pulse shapes caused longer latencies and higher resting motor thresholds (RMT) as compared to wider pulse shapes.
Conclusions: We can tune the aftereffects of rTMS by manipulating pulse width and directionality; this may be due to the different membrane properties of the various neuronal segments such as dendrites.
Significance: To date, rTMS frequency has been the main determinant of the plastic aftereffects. However, we showed that pulse width also plays a major role, probably by recruiting novel neuronal targets.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is considered a promising therapeutic tool in neuropsychiatric diseases and has demonstrated a definite efficacy in the treatment of depression and chronic pain [1]. However, there are patients who are resistant to rTMS therapy. This may be due to a differing sensitivity to rTMS [2]. To this date, the rTMS parameters contributing to such variability are not clear. A better understanding of the underlying mechanisms affecting the outcome of rTMS is expected to enhance its reliability as a therapeutic tool [3,4].

Variable rTMS aftereffects are thought to depend on different physiological mechanisms of the neuronal responses; intracellular due to alterations of Ca^{2+} spiking [5], extracellular by shifts in levels of factors and kinases [6], or on the network level by eliciting near and more distant related cortical potentials [7]. Various models have been proposed to combine the physical parameters of the stimulation and their various physiological interactions [8–10]. Those models address distinct parts of the pyramidal cells together with their connecting inhibitory neurons, primarily in order to

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model TMS effects on the temporal evolution of cortico-spinal volleys (direct and indirect waves), and to a lesser extent the expected plastic aftereffect in response to such stimulation. There is a multitude of proposed mechanisms for the therapeutic effects and this leads to ambiguity with regard to the neuronal mechanism of rTMS-induced plasticity, particularly when considering their interaction [11,12].

Only a few rTMS parameters involved in modulating its effects have been closely investigated, among which are e.g. stimulation frequency, intensity and number of pulses and sessions [1]. However, the impact of individual pulse shapes on rTMS outcome is unknown because technical limitations prevented systemic variation of pulse shape. Aside from rare exceptions we have only been able to change pulse frequency and patterns [13,14].

A controllable pulse parameter TMS (cTMS) device opens up a new parameter-space for TMS, i.e. pulse shape. It is capable of producing near rectangular pulse shapes by the use of two capacitors, and two bipolar semiconductor transistors that alternate the current between the capacitors [15]. The cTMS rectangular pulse platform provides a sufficient flexibility of pulse shapes by altering the phase widths, heights (intensity) and also the relation between positive and negative components of the pulse (directionality, defined as the M ratio). Such customized pulses may be more efficient [16] and could be applied in repetitive trains. In particular, symmetrical, bidirectional pulses, which require little or no capacitor discharging, can be applied at repetition rates of up to 1 kHz [13]. In this study, we made use of the cTMS to test the effect of pulse width and directionality on the sign and temporal evolution of plastic aftereffects.

Across a wide range of neuromodulatory protocols, AP current gives a more evident outcome in correlation with latencies. This was observed with numerous modalities of rTMS, e.g. continuous theta-burst stimulation (cTBS) [17,18], anodal transcranial direct current stimulation [19,20], short latency afferent inhibition protocol [21], and 5 Hz [22] and 1 Hz rTMS [23]. While this latency to after effects correlation was very strong in some cases to the extent of claiming the possibility of identifying responders from non-responders to cTBS based on it [17,18], this correlation however was not significant with 1 Hz rTMS [23]. In this study, 900 pulses of 1 Hz rTMS from a MAGpro stimulator produced plastic MEP changes only if the current was induced in the anteroposterior (AP) but not the posterioanterior (PA) direction. Biphasic, symmetrical pulses with the central, decisive AP-directed component induced facilitatory aftereffects, while monophasic AP-directed pulses produced inhibitory aftereffects [23].

This differing behavior in response to AP stimulation is probably because different populations of neurons are responding. This can be seen in recordings of the descending corticospinal volleys which showed that AP stimulation preferentially recruited late I waves while PA stimulation more readily recruited earlier I waves [24].

Using cTMS enabled D'Ostillio and colleagues to increasing the pulse width from 30 to 60 and then to 120 μs which led to a significant shortening of the latency but only with AP stimulation [25]. Additionally, 30 μs pulses applied in the AP direction in the short latency afferent inhibition protocol gave longer latencies and produced more inhibition than 120 μs pulses [26].

We were particularly interested in AP stimulation because only this orientation had produced plastic aftereffects in response to 1 Hz rTMS [23], and had shown significant variation in the latencies to different pulse widths [25].

In this study, we systematically explored the influence of pulse shape on the aftereffects of a low frequency (1 Hz) rTMS train, which is thought to induce inhibitory aftereffects [27,28]. We focused on pulse duration and pulse directionality, both of which presumably play an important role in the selective stimulation of neurons in the primary motor cortex (M1).

We used quasi-unidirectional pulses with an M ratio of 0.2 while varying the width of the main pulse component. The M ratio is a measure of directionality or asymmetry that expresses the ratio between the intensities of the first and second phase as shown in Fig. 1. We then kept the width of the main pulse component constant and compared the most asymmetrical, i.e. the quasi-unidirectional pulses with two other levels of pulse directionality (ratios of 0.6 and 1.0 M).

We also plotted the strength duration curve for the motor cortex by defining the pulse width threshold (PwTh) as the narrowest pulse width required to elicit a 50 μV MEP in five out of ten trials at 100% maximum stimulator output (MSO) of the cTMS intensity. We used 60 μs as a reference for the RTM defined it as 100% and then went in 10% steps into the widest possible pulse in one direction and the 100% MSO in the other.

Methods

Participants

Fifteen healthy volunteers were recruited for the main experiments (five males and ten females, mean age ± standard deviation was 25.2 ± 3.7 years). All participants were right-handed and free from any neurological or psychiatric disorders, took no centrally acting medications, and had no contraindications to TMS. Because the power cap of the device and the standard coil for the wider pulse shapes prevented intensities above 50% MSO, a higher resting motor threshold, i.e. above 70% MSO for the Magstim device was an exclusion criterion.

We obtained written informed consent from each subject before participation. The local ethics committee of the University Medical Center Göttingen approved the study protocol, which conformed to the Declaration of Helsinki.

Recordings

Motor evoked potentials (MEPs) were recorded from the first dorsal interosseous (FDI) muscle of the right hand with surface Ag–AgCl electrodes in a belly-tendon montage. The electromyography signals were amplified, band-pass filtered (2 Hz–2 kHz), and digitized at a sampling rate of 5 kHz with a micro-1401 AD converter (Cambridge Electronic Design Ltd., Cambridge, UK). All signals were stored in a computer for offline analysis. The peak-to-peak MEP amplitude served as an index for M1 excitability. The participants were asked to relax the right FDI during the measurements. If recordings were contaminated by voluntary muscle contraction before the TMS pulse(s), they were excluded from analysis.

A Magstim 200 (Magstim Co. Ltd., Whitland, UK) for measurement and a cTMS prototype 3 (cTMS3; Rogue Research Inc., Montreal, Canada) for intervention were used to deliver TMS over the M1.

- Initial session: motor thresholds and MEP latencies were measured using 25 pulses of AP 110% active motor threshold (AMT) for each pulse shape (Fig. 1).
- Five repeated, randomized sessions were separated by at least one week to avoid carry-over effects:
  Step 1: measuring the thresholds and the baseline:

For each session, we determined the Magstim RMT and the MSO intensity that gives approximately 1 mV amplitude for the pre-measurement intensity in the PA direction. In addition, we

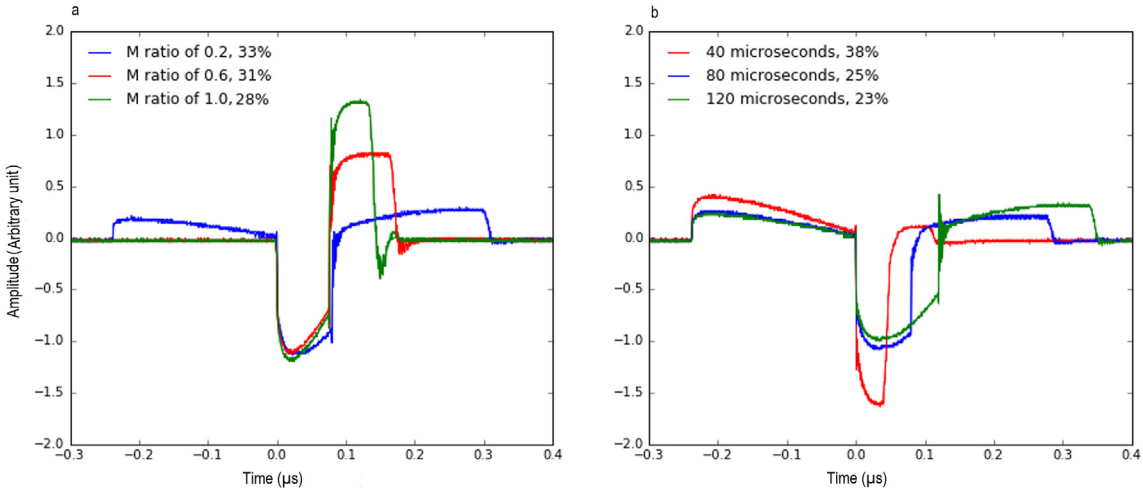

Fig. 1. Pulse shapes used in the 1 Hz stimulation as measured by an external pickup coil and oscilloscope, calibrated to the threshold level of each pulse shape expressed in percentage of the maximum stimulator output.

measured RMT for the cTMS pulse shape being used for the intervention in AP direction by rotating the coil 180°, and then we used 90% of that RMT for the rTMS in the same direction. The baseline measurement consisted of 50 pulses at 0.25 Hz with the previously determined 1 mV intensity.

Step 2: The interventional cTMS stimulation and in-between measurements as shown in Fig. 2: We applied 900 rTMS pulses at 1 Hz and 90% RMT intensity in five 180-pulse blocks separated by ten 1 mV MEP pulses using Magstim for the in-between measurement. The pulse shapes used were unidirectional with the main component in the AP direction with pulse widths of 40 μs, 80 μs, and 120 μs and a fixed 0.2 M ratio, as well as with different pulse directions, i.e. 0.2, 0.6 and 1.0 M ratios and a fixed width of 80 μs.

Step 3: After the final 180 rTMS pulse block, we recorded 25 pulses targeting a 1 mV amplitude every 5 min for 30 min using Magstim.

Statistical analysis: We averaged the RMT values and MEP latencies for each subject for each pulse shape. RMT was analyzed using repeated measures ANOVA with the pulse shape of TMS as the independent variable. To analyze MEP latencies, we averaged the 25 trials, and then we visually evaluated and marked the values. We analyzed the results using repeated measures ANOVA with the pulse shapes. For the MEP changes, we performed multiple paired, two-tailed t-tests on the MEP amplitudes from the normalized 1 mV baseline for each condition with the baseline, then we used Benjamini and Hochberg false discovery rate analysis for correction of multiple comparisons p values into Q values. For correlation analysis, we correlated MEP latencies and amplitudes across all data points using linear regression. The level of significance was set at $p < 0.05$.

After data analysis, the pulse width threshold was determined in a separate session in eleven of the fifteen participants. This was done by defining the RMT at 60 μs.as 100% and then increasing or decreasing in 10% steps until the limits of the stimulator were reached; pulse width of 120 μs in one direction and 100% MSO in the other. We defined the pulse width threshold as the shortest pulse width at 100% MSO that produced MEPs with a 50-μV amplitude in five out of ten trials. We correlated the PwTh to the average MEP change for each subject using linear regression.

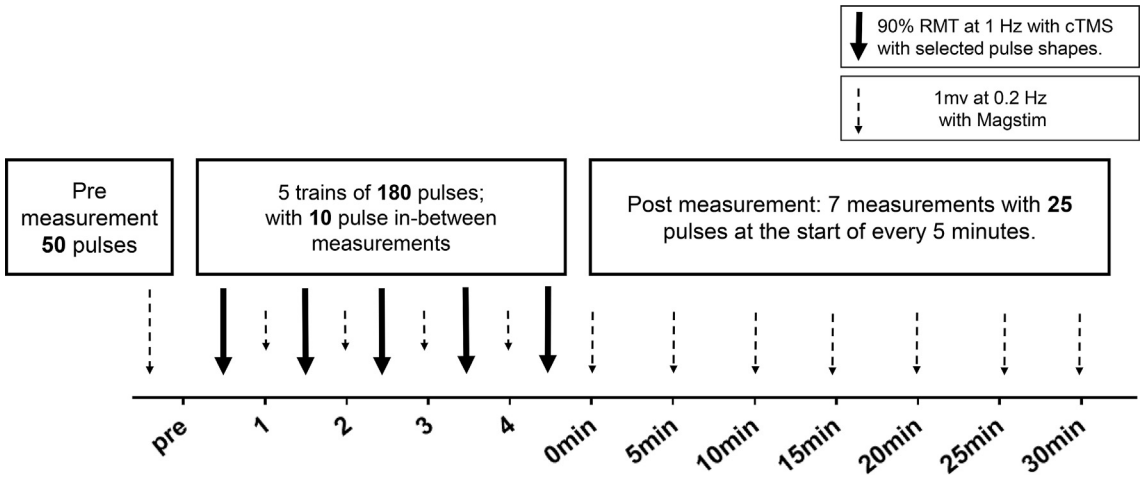

Fig. 2. Diagram of the experiment timeline for each session. Each subject had five such sessions, one with each pulse shape.

Results

RMT: Longer pulse shapes had lower RMTs than shorter pulse shapes. Pulse width F value was 232.5 with $p < 0.0001$ (Fig. 3a). Pulses with a higher M ratio had a lower threshold than quasi-monophasic pulses. M ratio F value was 75.97 with $p < 0.0001$. (Fig. 3b).

Latencies: AP latencies were significantly longer for the narrower pulse shapes, particularly for the 40 μs pulse shape, which had the longest latency of all examined pulse shapes with a mean of 22 ± 1.2 ms. The 80 μs pulse shape had a mean latency of 21.3 ± 1.1 ms., and the 120 μs pulses expressed the lowest latency of the monophasic pulses with a mean latency of 20.5 ± 0.9 ms. Pulse width F was 27.23 with $p < 0.0001$. (Fig. 4a).

For directionality, pulses with an M ratio 0.2 had the longest latency with a mean of 21.3 ± 1.1 ms. M ratio of 0.6 had a mean latency of 19.8 ± 1.1 ms, and M ratio of 1 had the shortest latency of all tested pulse shapes with a mean of 19.4 ± 1.0 ms. M ratio F was 23.29 with $p < 0.0001$ (Fig. 4b).

Plastic aftereffects: We plotted the averaged normalized MEP data in the pre-stimulus, baseline phase, during stimulation [1,2,3and4] and after stimulation (0 min−30 min). We compared all subsequent data points to the baseline using a multiple comparison, paired *t*-test.

Shorter, monophasic pulses with a main component duration of 40 and 80 μs induced predominantly significant inhibition ($q < 0.001$, corrected paired two tailed *t*-test) at all of the time points during and after stimulation when compared to the baseline. The 120 μs pulse shape showed a different pattern that tended towards excitation. But this was only significant from the 15 to the 30 min time points ($q < 0.001$, corrected paired two tailed *t*-test) (Fig. 5).

As for the M ratio plastic aftereffects, pulses with an M ratio of 1.0 produced inhibition during stimulation ($q < 0.001$, corrected paired two tailed *t*-test). The effect shifted to excitation at the 25 min time point ($q < 0.001$, corrected paired two tailed *t*-test) (Fig. 6). An M ratio of 0.6 induced minor inhibition, but only during stimulation at the in-between measurements ($q < 0.02$, corrected paired two tailed *t*-test) with no further significant shift from the baseline. The 0.2 M ratio induced significant inhibition ($q < 0.001$, corrected paired two tailed *t*-test) at all the data points up (Fig. 6). Note that the 0.2 M ratio data is the same as in the pulse width comparison with the 80 μs pulse.

We correlated the average increase in MEPs across all time points to the latency differences using linear regression analysis and found no significant correlation for the different pulse widths (Fig. 7a, b).

Using the pulse width threshold data, we plotted a pulse width/strength (MSO %) curve by defining the RMT at 60 μs.as 100% and then shifting it in 10% steps in both directions. The limits of the stimulator were reached, with a pulse width of 120 μs of the main pulse component in the longer pulse direction and 100% MSO in the shorter one. In the latter, PwTh ranged from 17 to 26 μs (Fig. 8a). We then plotted its correlation with the average MEP percentage change for 40, 80 and 120 μs. The 40 μs showed significant negative correlation with an r value of −0.71 and a P value of 0.0145 demonstrating that subjects with higher PwTh values had more inhibition in response to shorter pulse stimulation. (Fig. 8b).

Discussion

Many approaches are currently in use to improve the efficacy of rTMS. In this study one of our aims was to elucidate the effects of prolonging the pulse duration of a unidirectional pulse from 40 μs to 120 μs, which is now technically possible with the recently developed cTMS device [13]. A secondary goal was to study the underlying mechanisms of current flow direction by changing the pulse shape from unidirectional to bidirectional while keeping the pulse duration constant. We used a repetition rate of 1 Hz, a protocol that robustly produces inhibitory aftereffects [28]. We applied rTMS in the anteroposterior direction as defined by the higher single pulse threshold as compared with PA direction. At the 1 Hz repetition frequency we reproduced the inhibitory effects of conventional TMS with short unidirectional AP pulses and the facilitatory effects of bidirectional AP pulses [23]. The novel key finding is that 1 Hz rTMS with 120 μs wide unidirectional pulses increased cortical excitability although significance was reached only 15 min after the end of the stimulation.

To our knowledge this is the first study to systematically and independently alter one pulse parameter (duration or directionality ratio) while keeping the other constant. Our results are in agreement with those in the available literature. Our 80 μs unidirectional pulse, which is identical to the "RU-N" pulse applied at 1 Hz by Goetz and colleagues [29], caused robust inhibition very similar to the effect they reported. Also the inhibitory aftereffects found in numerous studies using conventional TMS pulses at 1 Hz [28,30] compare very well with the effects we observed with 40 and 80 μs

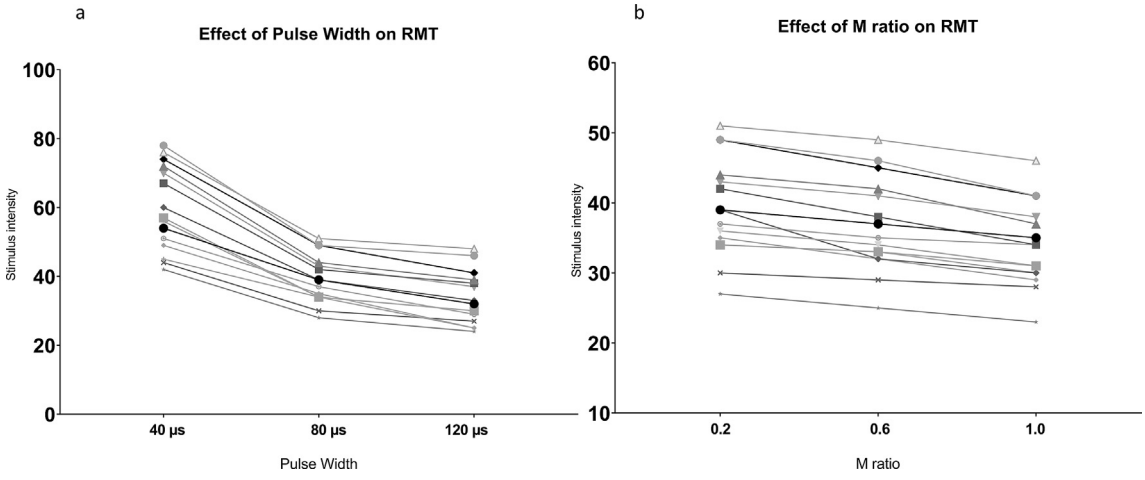

Fig. 3. Effect of pulse width (a) and directionality (b) on resting motor threshold.

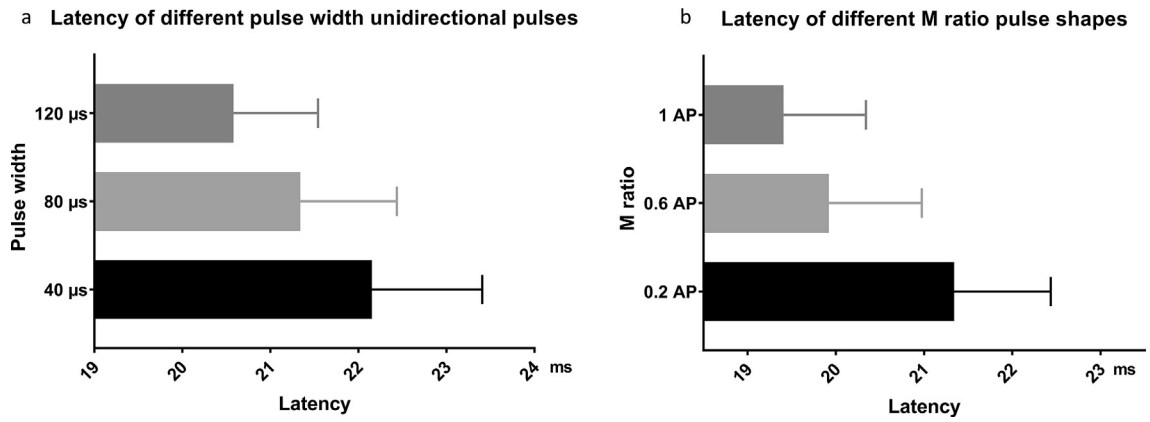

Fig. 4. Anteroposterior latencies for pulse shapes with different pulse widths (a) and M ratio (b).

unidirectional pulses. Thus, our finding of excitatory rather than inhibitory aftereffects with the 120 µs pulses was not anticipated and requires further investigation of the underlying physiological mechanisms of rTMS aftereffects.

In all subjects, RMT (Fig. 3) and MEP latency (Fig. 4) decreased with increasing pulse width and directionality, i.e. increasing M ratio. The completely bidirectional pulse shape had the shortest latency, which was similar to PA latencies. This supports the notion that not the first 'negative' phase of the bidirectional pulse but the second 'positive' PA-oriented phase of the pulse may have had determined latency and threshold [31].

The lower threshold of longer pulses as described by Ref. [25] is associated with a higher total pulse energy [32,33]. However, the higher pulse energy alone could not account for the shift from inhibitory to excitatory plastic aftereffects. Earlier studies that tested 1 Hz rTMS applied with constant pulse duration, reported that an increase in the pulse amplitude above the 90% RMT used here, resulted in even stronger inhibition [34–36].

The aftereffects seem to differ to some extent from intra-stimulation effects. All three directionality conditions induced inhibition during stimulation. This persisted after the unidirectional pulses but there was a shift to post stimulation facilitation with the fully bidirectional pulses. Most likely, the unexpected shift from intra-stimulation inhibition to post-stimulation facilitation with bidirectional pulses is caused by the second pulse phase. We propose that both the first and the second phase induce a paired pulse stimulation effect. This may either occur by the simultaneous induction of spike-time dependent plasticity in various nearby neurons at the network [37] or the neuronal level [38]. This could occur if one phase stimulated the axon hill or the axon at the bend in the white matter and the second one preferentially targeted dendrites [39]. Dendritic morphology and synapse locations has been found

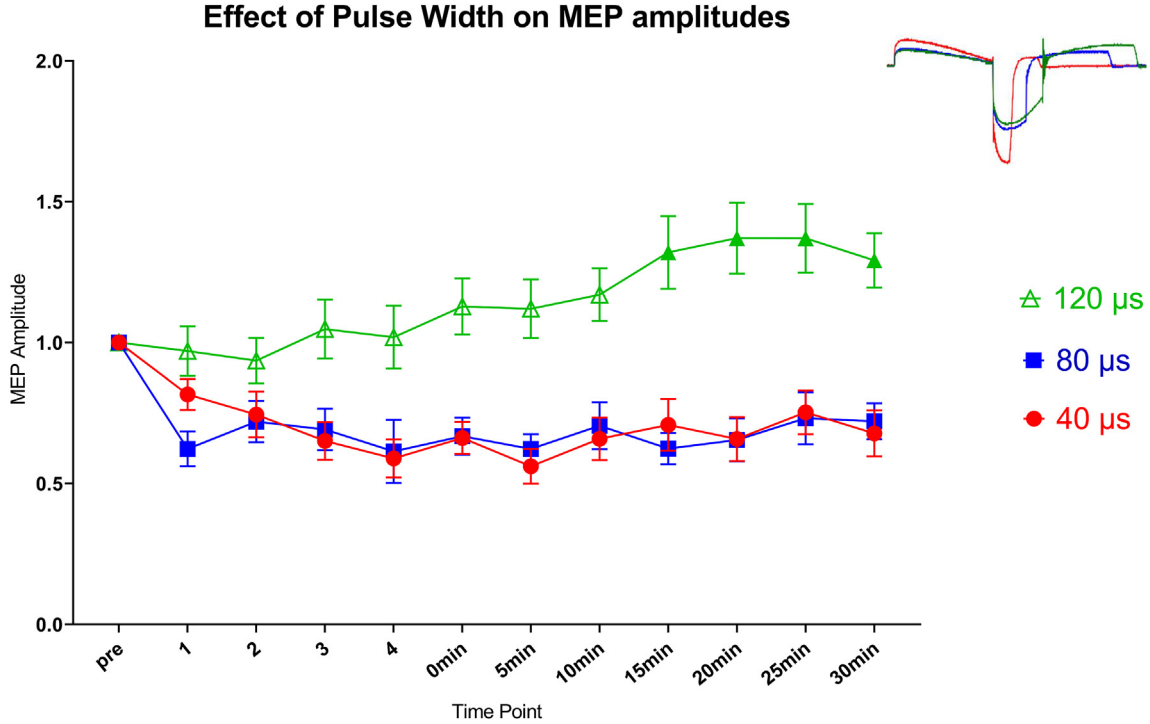

Fig. 5. Aftereffects of 1 Hz AP stimulation using monophasic pulses with 40, 80 and 120 µs main component durations, pulse shapes are illustrated in corresponding colors in the top right panel. Solid shapes indicate significance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

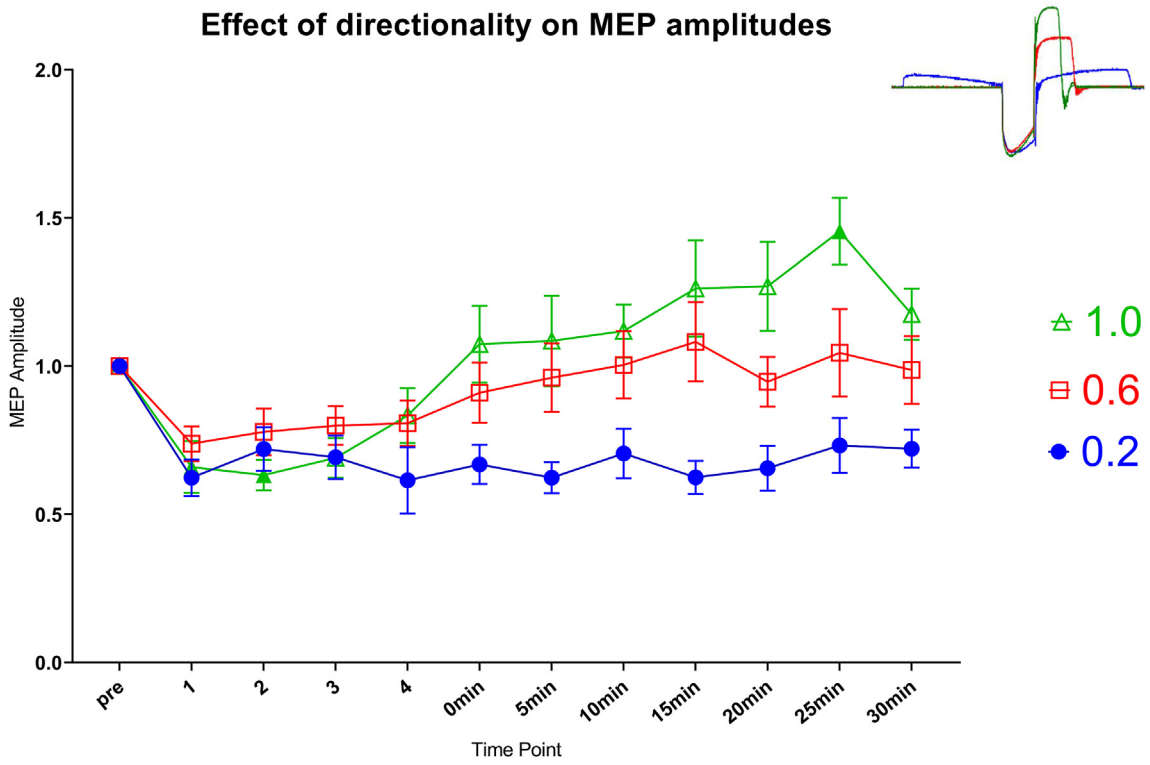

Fig. 6. Aftereffects of 1 Hz AP stimulation using 80 μs pulses with m ratios of 0.2, 0.6 and 1. Pulse shapes are illustrated in corresponding colors in the top right panel. Solid shapes indicate significance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

to affect the spike-time dependent plasticity [40]. Another explanation would be that the inhibition induced by the monophasic 0.2 M ratio pulses could be attributed to repeated hyperpolarization of pyramidal cells, while the biphasic 0.6 and 1.0 M ratio pulses induced a similar initial hyperpolarization followed by a steeper polarization [14] thus producing some facilitation.

As described by Ref. [23] we were also unable to detect a correlation between the modulatory effect strength of 1 Hz rTMS and MEP latencies. This differs from the results of studies on cTBS [17,18] or anodal tDCS [20,26] which showed a significant correlation between AP MEP latencies and the neuromodulatory outcome of those protocols. We understand that this correlation is not intuitive, but the previous significant correlation with cTBS aftereffects attempt to identify a possible biomarker for plastic aftereffects (17,18) and the different latencies of different pulse widths [25], lead us to examine if this variability in latency in response to

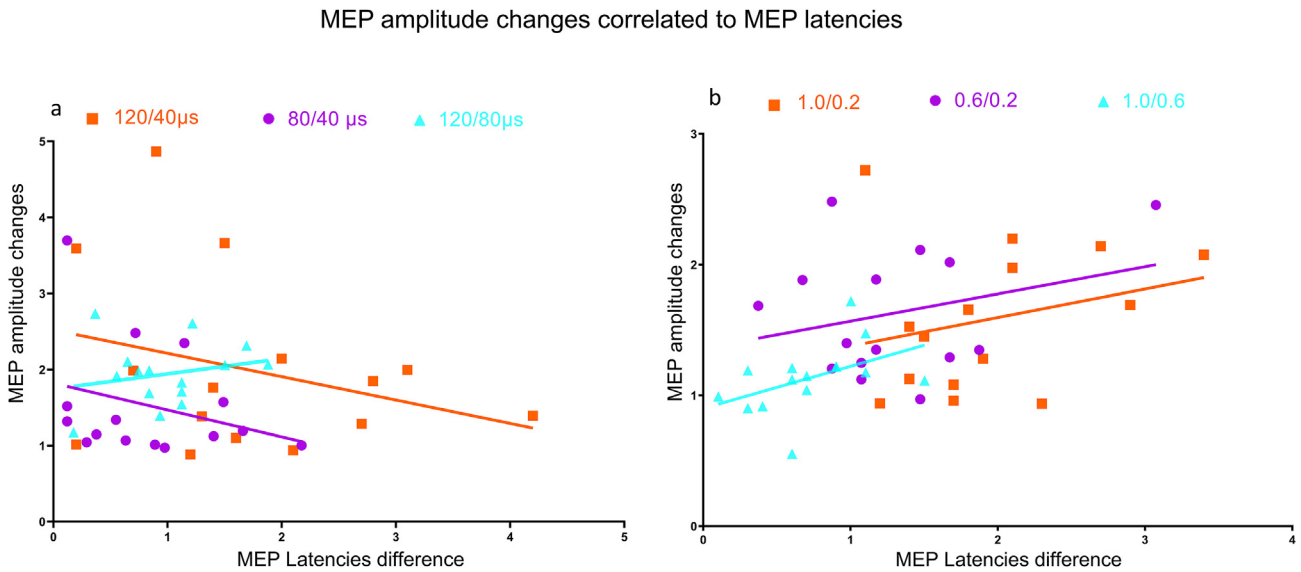

Fig. 7. Correlation between the average change in MEPs across all time points and the latency differences among: a) different pulse widths and b) different M ratios. There was no significant correlation.

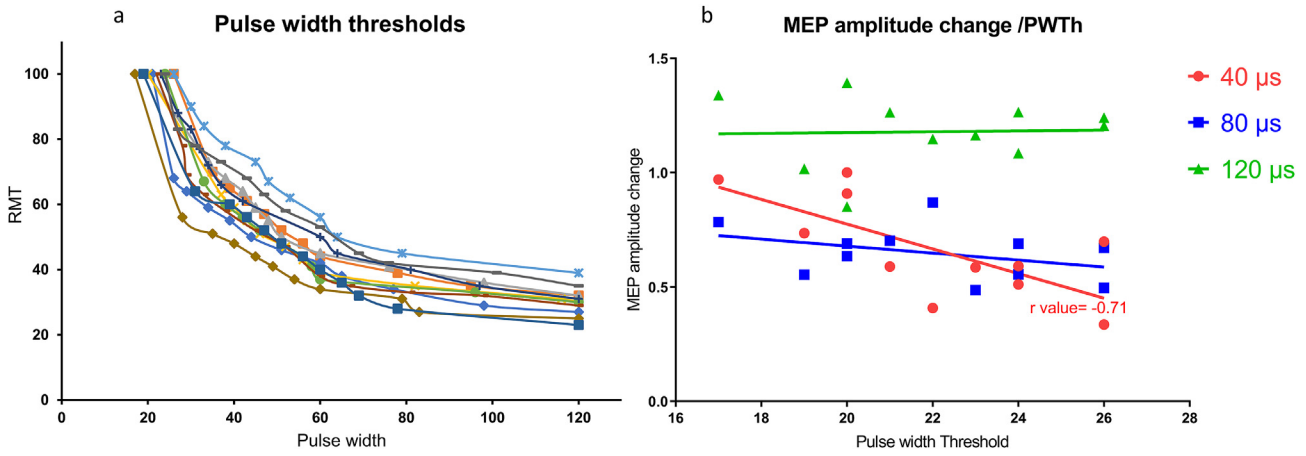

Fig. 8. a) Pulse width/strength RTM curves for eleven subjects. b) Correlation between the average change in MEPs across all time points and the PwTh, only the 40 µs condition showed significant negative correlation.

different pulse shapes would also act as a determinant for plastic aftereffects. A neurocomputational model by Rusu and colleagues showed that increase of dendrite length and concentration lead to a higher spiking rate [10], explaining how wider pulses have shorter latencies through summation of dendritic spikes.

It was demonstrated experimentally [41,42] and by modelling [43] that axons have orientation specific threshold as neuronal fibers respond more readily to perpendicular currents [44]. If we transfer this effect to the in vivo setting, this could attest that dendrites and smaller branching axons have a higher likelihood of responding to stimulation in any direction and thus also to AP stimulation with a smaller percentage of larger axons being stimulated as those have a higher threshold in this orientation [45]. So even though dendrites generally have a higher threshold and require more energy to be stimulated, the threshold of axons can exceed the dendritic threshold in certain orientations.

Lee and Fried used an implanted micro magnetic coil to selectively stimulate cultured layer 5 neurons to demonstrate that tuft dendrites were harder to stimulate, as in they required a longer stimulation duration of the same intensity 10 Hz stimulation [41]. However, when finally activated, the firing was higher in amplitude and outlasted the magnetic stimulation. While axonal stimulation only resulted in firing during the stimulation, indicating that dendrites have more plasticity than axons [41]. This emphasizes the significance of dendritic stimulation in producing lasting aftereffects even at the single neuron level. It is already known that higher frequency stimulation increases excitability, and if prolonged can lead to epileptic fits [12]. And conversely, patients with epilepsy have been found to carry genes for abnormal dendritic spines, branching and arborization [46].

Changes in thresholds, latencies and the inversion of aftereffects all suggest that wider and bidirectional TMS pulses are recruiting additional neuronal targets. In experiments and biophysical models of neurons and neural compartments a strength-duration analysis of excitability has proven useful to study recruitment of different neuronal targets [42,47]. In such analysis, rheobase is defined as the minimum intensity required to trigger a response to arbitrarily long stimuli. The chronaxie is defined as the minimal pulse width that can still trigger a response, if the stimulus intensity is set to twice rheobase.

In this study we tried to fully plot the strength duration curve for the human primary motor cortex (Fig. 8a). Since the width of the determinant phase of the cTMS pulse shapes has an upper limit of 120 µs, we were unable to obtain data on the rheobase of the motor cortex. The graph in (Fig. 8a) shows different slopes across the range of pulse widths from 20 to 120 µs, which might suggest that at least two different neuronal populations with different chronaxies are being stimulated. This is however uncertain as it impossible to isolate those effects on the strength duration curve as in neuronal culture results simply because the brain has a much more complicated neuronal architecture.

The properties of our two shorter unipolar pulse shapes with 40 and 80 µs resemble most closely the conventional monophasic pulse shape produced by the Magstim device with a main component of 82 µs [48] which failed to produce any firing in layer 5 dendrites in the mouse cortex [49] also being in line with the existing literature on conventional pulses [27,28].

The shorter pulse duration end of the strength duration curve signifying our PwTh (the pulse width below which it is not possible to excite the neuron) varied with our equipment between 17 µs and 26 µs (Fig. 8a). In a neuronal model, pulse width shorter than 100 µs was not able to stimulate dendrites any more, while the axon and soma were still responsive for pulses as short as 10 µs [47]. Accordingly, our 120 µs pulse shape should have the highest likelihood of stimulating dendrites.

We found a significant negative correlation between the PwTh (at 100% MSO) and the plastic aftereffects of the 40 µs conditions as subjects with higher PwTh had more inhibition (Fig. 8b). Since we assume that 40 µs only stimulate axons or the cell body this might reflect individual variation of percentages of larger axons and smaller branches and dendrites at the stimulated area.

Here we propose that AP stimulation more readily target dendrites, as dendrites do not have a particular orientation as axons. The selective membrane properties of the dendrites render anteroposterior stimulation more sensitive to temporal TMS parameters, producing those differences in latencies, thresholds and plastic aftereffects in response to different pulse widths and directionalities. This might be the underlying reason for increased excitability in response to wider pulse rTMS. If that is true, we could lead to more fine tuning of the aftereffects of different stimulation protocols theoretically through activation of different neuronal components.

Role of the funding sources

The funding sources had no involvement in the conduct of the research, the collection, analysis and interpretation of data; in the

writing of the report; and in the decision to submit the article for publication.

Declaration of interest

None declared.

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