Wider pulses and higher intensities increase efficiency of high frequency rTMS

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Abstract:

Introduction: High frequency repetitive transcranial magnetic stimulation induces excitation when applied to the motor cortex, as measured by increased amplitudes of motor evoked potentials (MEPs) after the intervention. Different pulse widths induce different effects, likely by primarily stimulating distinct segments of neurons due to the different membrane properties of different neuronal segments. Here we focus on the aftereffects generated with high frequencies of controllable pulse TMS (cTMS).

Objectives: To investigate the influence of different stimulation intensities, pulse widths and direction of high frequency rTMS on its excitatory plastic aftereffects as reflected by MEP amplitudes.

Methods: Using a controllable pulse stimulator TMS (cTMS), we stimulated the hand motor cortex of 20 healthy subjects with 5 Hz rTMS with 1200 bidirectional pulses with the main component widths of 80 and 120 microseconds. 80% resting motor threshold (RMT) intensity was investigated for both directions anterior-posterior (AP) and vice versa (PA), and at 90% RMT in the AP direction for the second experiment.

Results: 80% HF rTMS did not produce any significant excitation in both AP and PA directions. 90% RMT AP stimulation exhibited a significant excitation aftereffect with the 120 microseconds wide pulses, whereas the 80 microseconds failed to produce significant excitation.

Conclusions: Higher intensity and longer HF pulse rTMS are more efficient in producing excitatory aftereffects, this may be due to the different membrane properties of the various neuronal segments such as dendrites whose activation plays a major role in long term potentiation.

Significance: The findings here may contribute to better results in future clinical studies performed with longer cTMS pulses.

Introduction:

Therapeutic use of repetitive transcranial magnetic stimulation (rTMS) has been shown to have level A efficacy in treatment of depression and chronic pain treatment (Lefaucheur et al., 2014). More efficacious protocols are needed and are e.g. subject of two ongoing NIH research initiatives. Key rTMS parameters involved in its efficiency are stimulation frequency, intensity and number of pulses and sessions have been closely investigated (Rossini et al., 2015). However, the impact of individual pulse widths on rTMS outcome is under investigated because of the scarcity of devices that could readily change the pulse widths. Now we have the technology to change pulse widths as easy as to change pulse frequency and patterns (Peterchev et al., 2011).

The controllable pulse parameter TMS (cTMS) device can manipulate the pulse width of its near rectangular pulse shapes by the use of two capacitors, and two bipolar semiconductor transistors alternating current between the capacitors (Peterchev et al., 2014). Such customized pulses may be more efficient in delivering energy to the cortex making use of the leaky properties of neuronal membranes (Goetz et al., 2013), and they could be applied in repetitive trains. Here, we use cTMS to test the effect of different pulse widths on the excitatory aftereffects of HF rTMS. With lower rTMS frequency of 1 Hz and using cTMS we have already shown that only the widest pulse shape of 120µs lead to a significant increase excitability, while the two shorter pulses shapes of 40 and 80 Hz produced significant inhibition (Halawa et al., 2019).

In this study, we explore the interplay of coil direction, pulse width and intensity on the aftereffects of high frequency (5 Hz) rTMS train, a protocol well known to induce excitatory aftereffects (Hallett, 2007; Ziemann et al., 2008).

Figure 1: Diagram of the experiment timeline for each session of the experiment.

***Methods*:**

Participants

For the first experiment, we recruited fourteen subjects, four males and ten females, mean age was 23.5 ± 2.6 SD years. For the second experiment, a different set of fifteen healthy volunteers was recruited, four males and eleven females, the mean age was 24.1 ± 3.1 SD 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% of maximal stimulator output (MSO), a higher resting motor threshold, i.e. above 70% MSO for a Magstim 200[2] 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 individual traces were contaminated by voluntary muscle contraction before the TMS pulse(s), they were excluded from the analysis.

A Magstim 200^2 (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.

Repeated, randomized sessions were separated by at least one week to avoid carry-over effects, four sessions first experiment and two for the second one (fig 1):

Step 1: measuring the thresholds and the baseline:

For each session, using the Magstim 200^2 with the D70 coil we determined the RMT and the MSO intensity that gives approximately 1 mV amplitude for the pre-measurement intensity in the PA direction. In addition, we measured RMT for the cTMS pulse shape being used for the intervention in both PA and AP directions to use as reference for the 5 Hz rTMS intensity, by rotating the coil 180 degrees. The baseline measurements consisted of two 25 pulse measurements at 0.25 Hz with the previously determined 1 mV intensity.

Step 2: The interventional cTMS stimulation:

In order to isolate the effect of just increasing the pulse width and not having our effect contaminated by the directionality of individual pulses, we decided to use custom balanced bidirectional pulse shapes which are easier to fire in higher frequencies (Peterchev et al., 2011). We varied the main component from 80µs to 100µs and 120µs in PA and AP directions as shown in Fig 2. We used 80% of that RMT for the rTMS in

the corresponding direction. For the second experiment, we used 90% RMT of 80 and 120µs pulse shapes for the 5 Hz rTMS only in the AP direction.

We externally triggered the cTMS machine at 5Hz from an external trigger to fire those customized pulse shapes. For the first experiment we applied 1200 rTMS in both AP and PA directions at 5 Hz and 80% RMT intensity structured as six 200-pulse blocks with 15 MEP measurements in between as breaks necessary to produce significant excitatory aftereffects (Rothkegel et al., 2010). For the second experiment, we used the same protocol but with 90% RMT instead of 80% in the antero-posterior (AP) direction which is more efficient with 5Hz rTMS (Sommer et al., 2013).

Step 3: After the final rTMS pulse block, we recorded 25 pulses with the same baseline measurement intensity targeting 1 mV amplitude every five minutes for 30 minutes using Magstim 200[2].

Figure 2: Pulse shapes as measured by an external pickup coil and oscilloscope, used in the: a) 5 Hz PA Stimulation. b)5 Hz AP Stimulation

Statistical analysis: We averaged the RMT values for each subject for each pulse shape. RMT was analyzed using repeated measures ANOVA to test the significance of changing the pulse widths. For the MEP changes we used multiple way ANOVA for the pulse width, stimulation direction and evolution across for baseline and after measurement time points. Then for each time point, we performed post-hoc 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 Bonferroni-Dunn method for correction of multiple comparisons p values.

***Results*:**

RMT: For the first experiment longer pulse shapes had lower RMTs than shorter pulse shapes in PA direction with $p<0.0001$ (Fig 3.a) and AP direction with $p<0.0001$ (Fig 3.b). The same was true for the second group of subjects with the 80 and 120µs pulse shapes used for the 90% RMT AP 5 Hz rTMS $p<0.0001$. (Fig 3.c).

Figure 3: Effect of pulse width on the thresholds for individual pulse shapes used for 5Hz rTMS: a) PA directed for the three pulse widths used in the first experiment, b) AP directed for the three pulse widths used in the first experiment, c) AP directed for the two pulse widths used in the second experiment.

Plastic aftereffects: We plotted the averaged normalized MEP data in the baseline phase, during stimulation and after stimulation (0 min to 30 min). We used ANOVA to detect significance of changing the pulse width. We also compared all subsequent data points to the baseline using corrected multiple comparison, paired t-tests.

For the first experiment, ANOVA revealed that 80% RMT PA directed 5 Hz rTMS did not produce any significant aftereffects outlasting the stimulation and there was no significant effect of changing the pulse widths of PA with P value>0.1 (Fig.4). For AP directed stimulation, even though no significant effect of evolution across time points was found (P value=0.4769 and F=0.9530) and no significant shift from the baseline for

any time point using multiple t tests with adjusted P value>0.2 (Fig.5), there was a significant effect of pulse width change with P value<0.001 and F=12.76. Additionally, AP directed stimulation produced significantly more excitation than PA directed stimulation, P value<0.05 and F= 0.9826. Post-hoc multiple paired t tests showed no significant difference across all time points. No significant difference was found within the baseline measurements.

Figure 4: Aftereffects of 80% RMT 5 Hz stimulation using 80,100 and 120 µs main component in PA direction. Pulse shapes used for stimulation are illustrated in corresponding colors in the top right panel.

Figure 5: Aftereffects of 80% RMT 5 Hz stimulation using 80,100 and 120 µs main component in AP direction. Pulse shapes used for stimulation are illustrated in corresponding colors in the top right panel.

For the second experiment, 2-way ANOVA revealed significance of interaction between pulse widths with P value=0.0278 and F= 4.876 and evolution across time points P value=0.0135 and F=2.098. Post-hoc t tests showed that the 120 µs wide pulse shape produced significant excitation at six time points (corrected p <0.009, paired two tailed t-test), in comparison to the 80µs, which only produced significant excitation only at one time point (corrected p= 0.02, paired two tailed t-test). (Fig.5). No significant difference was found within the baseline measurements.

Figure 6: Aftereffects of 90% RMT 5 Hz AP stimulation using 80 and 120 µs main component durations, pulse shapes are illustrated in corresponding colors in the top right panel. Solid shapes indicate significance.

***Discussion*:**

In this study we succeeded in showing that prolonging the pulse duration of HF rTMS led to significant excitation for 90% RMT 5 Hz AP rTMS. For the first experiment we applied 80% RMT 5 Hz rTMS in both direction with pulse width of 80, 100 and 120µs with no significant aftereffects. Still we could conclude based on the ANOVA results from the first experiment that AP stimulation is more sensitive to pulse width change (P value<0.001) and more efficient in producing plastic after effects when compared to PA stimulation (P value<0.05), as demonstrated across many rTMS protocols especially for 5 Hz rTMS (Rothkegel et al., 2010; Sommer et al., 2013).

So, for the second experiment, we decided on using only the AP directed stimulation, increasing the intensity from 80% to 90% RMT with the widest 120µs and shortest 80µs pulse shapes. Again, we reproduced the excitatory effects of bidirectional AP pulses when provided in an interval design and not continuously (please note reversed denomination of pulse components in that paper) (Rothkegel et al., 2010). However, the novel key finding is that 5 Hz rTMS with 120 µs wide pulses increased cortical excitability more than the 80µs wide pulse 5 Hz rTMS.

In all subjects, RMT (Fig 3) decreased with increasing pulse width in congruence with previous works (D'Ostilio et al., 2016). While thresholds decreased apparently as read out by the MSO% of the device, that statement is only partially accurate because the stimulator just displays the intensity as reflected by the height of the pulse shape and not the total energy of the pulse which is expressed by the area of the pulse shape. Principally, wider pulses need more energy to elicit responses at the cortex (Barker et al., 1991; Peterchev et al., 2013; Grill, 2015). The higher total pulse energy could explain the wider pulses' seemingly higher efficiency when only referring to pulse amplitude (Modugno et al., 2001). As an analogue in rabbit cortices, high frequency stimulation needed pulses longer than 100µs to significantly potentiate neurons (McNaughton et al., 1978). However, pulse width cannot entirely substitute intensity, since increasing the pulse width of 1 Hz rTMS changed its expected inhibitory outcome into excitation (Halawa et al., 2019). Opposite to the known effect of increasing the intensity of 1 Hz rTMS that increases inhibition (Fitzgerald et al., 2002; Lang et al., 2006; Nojima and Iramina, 2017).

Neuronal models examining membrane properties for different parts of the neuron showed that pulse widths shorter than 100µs are usually not able to stimulate smaller dendrites with exceedingly high amplitudes, while the axon and soma are still responsive for pulses as short as 10µs (Rattay et al., 2012). As dendrites lack myelin (Aberra et al., 2018) and have a small diameter (Pashut et al., 2011), they respond preferentially to wider pulses. That could insinuate that pulse shapes wider than 100µs should have a higher likelihood of stimulating dendrites.

While dendrites are more difficult to activate, when they are eventually activated, they fire in higher amplitudes and for a longer period after cessation of stimulation (Lee and Fried, 2017), demonstrating that dendrites have more plasticity in comparison to axons. A similar effect was shown in single neurons where current injection in dendrites furthest from the soma produced longer and larger action potentials in comparison to somatic current injection (Larkum et al., 2007), especially in response to higher frequency and longer pulse widths stimulation (Ledergerber and Larkum, 2010).

Those special plastic properties could be mediated through their high resistance spines which allow them to passively amplify local synaptic depolarization up to 50 folds, where higher spine neck resistance lead to increased cooperativity (Harnett et al., 2012). The number of those dendritic spines also increased in response to high frequency rTMS (Vlachos et al., 2012).

Dendritic stimulation also produces back propagating potentials that would potentiate the anterograde potentials arising from somatic stimulation, thus producing LTP through associativity (Larkum, 2004) or cooperativity and spike timing dependent plasticity (Lenz et al., 2015). This was supported by the fact that distal dendritic

stimulation was more efficient in producing cooperativity LTP when compared to proximal dendrite stimulation (Weber et al., 2016).

Through different mechanisms, the significance of dendritic stimulation in producing outlasting plastic aftereffects through LTP in response to rTMS is emphasized (Sjöström et al., 2008; Müller-Dahlhaus and Vlachos, 2013). Here we show that wider pulses could increase the efficiency of excitation of HF rTMS probably through more dendritic activation, because of their unique membrane properties and important role in inducing synaptic plasticity.

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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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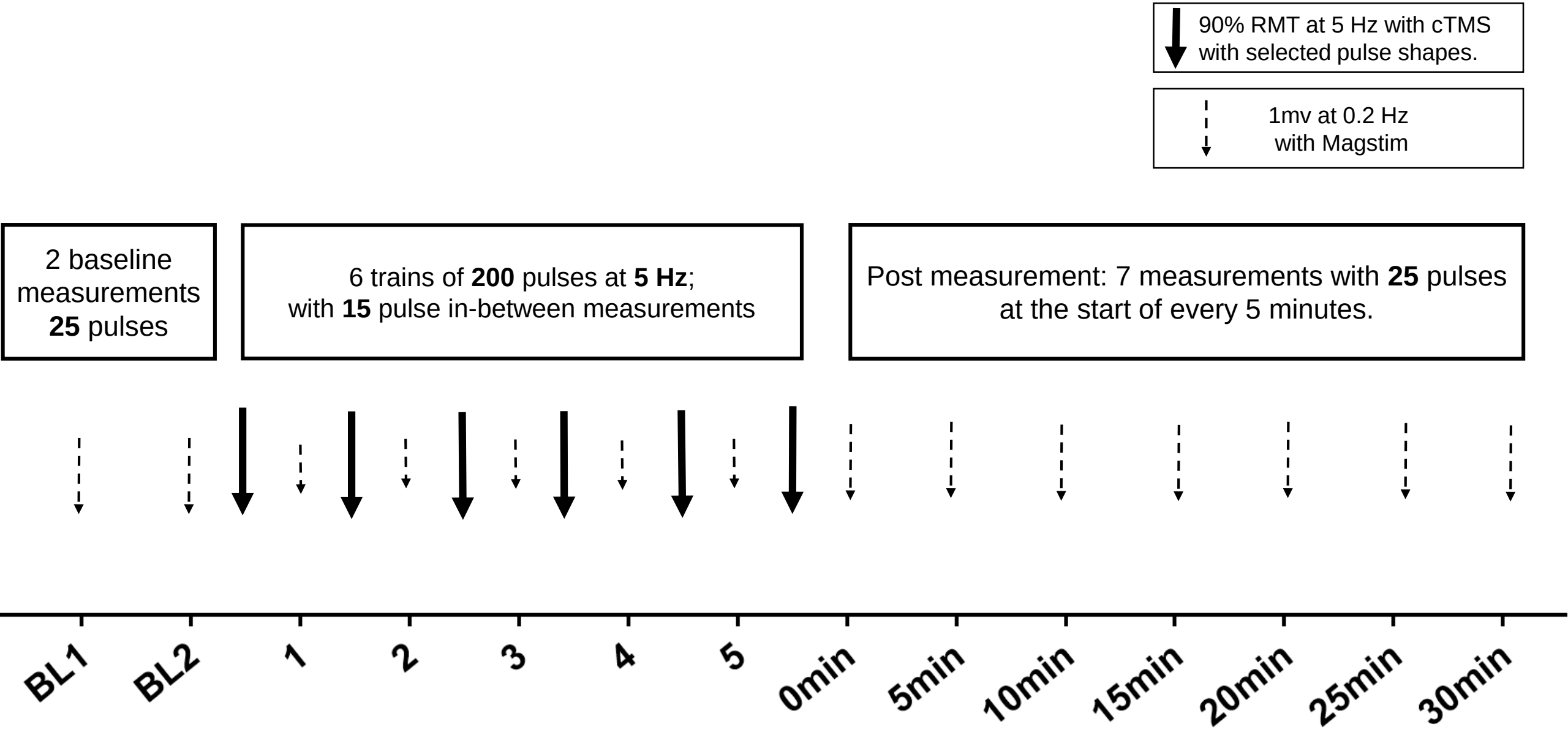
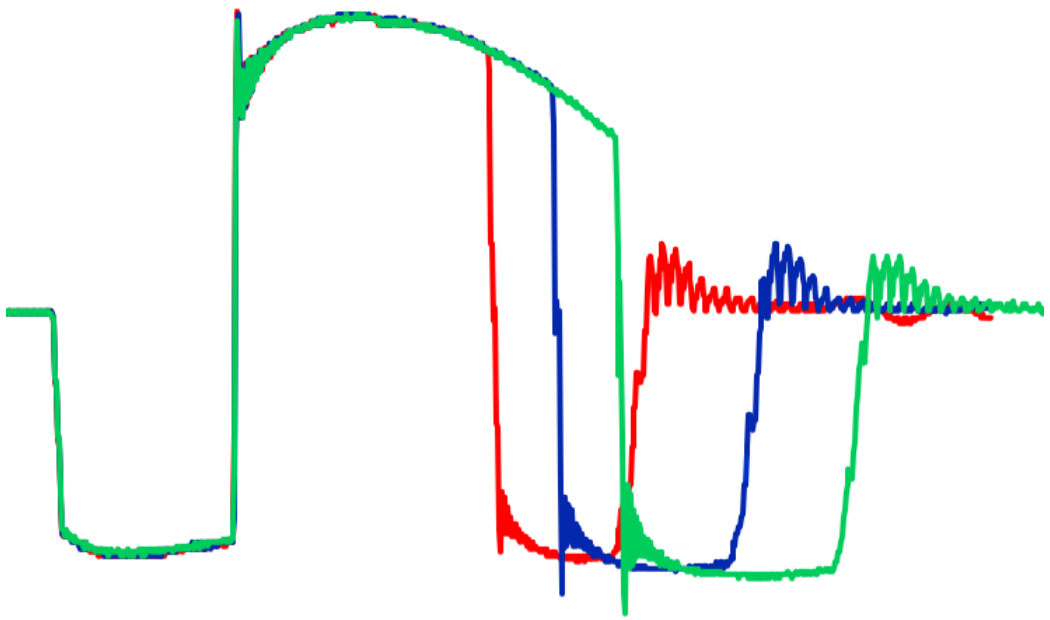
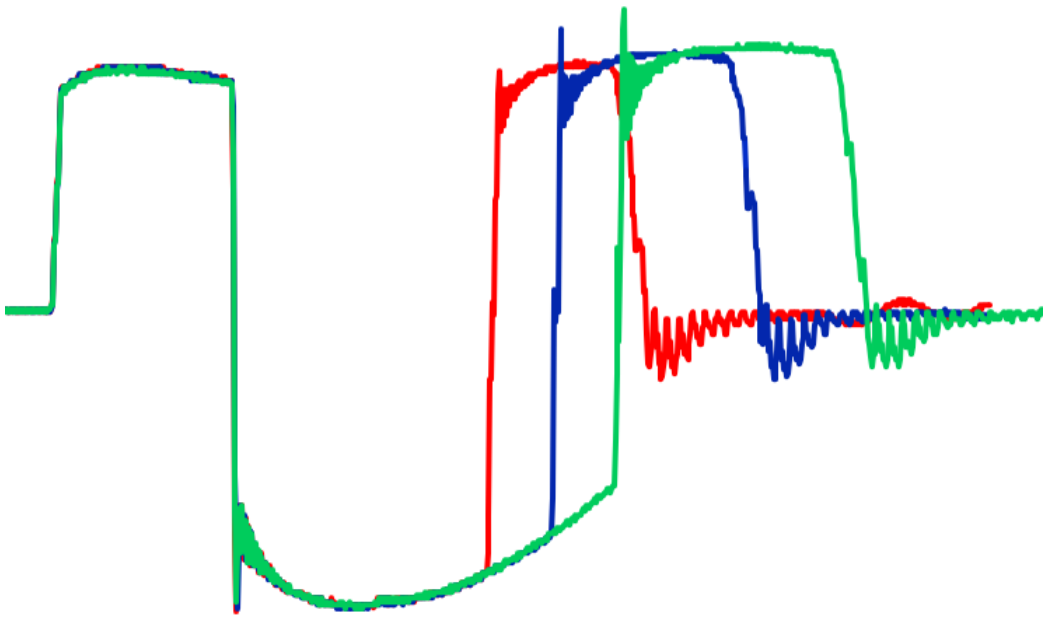
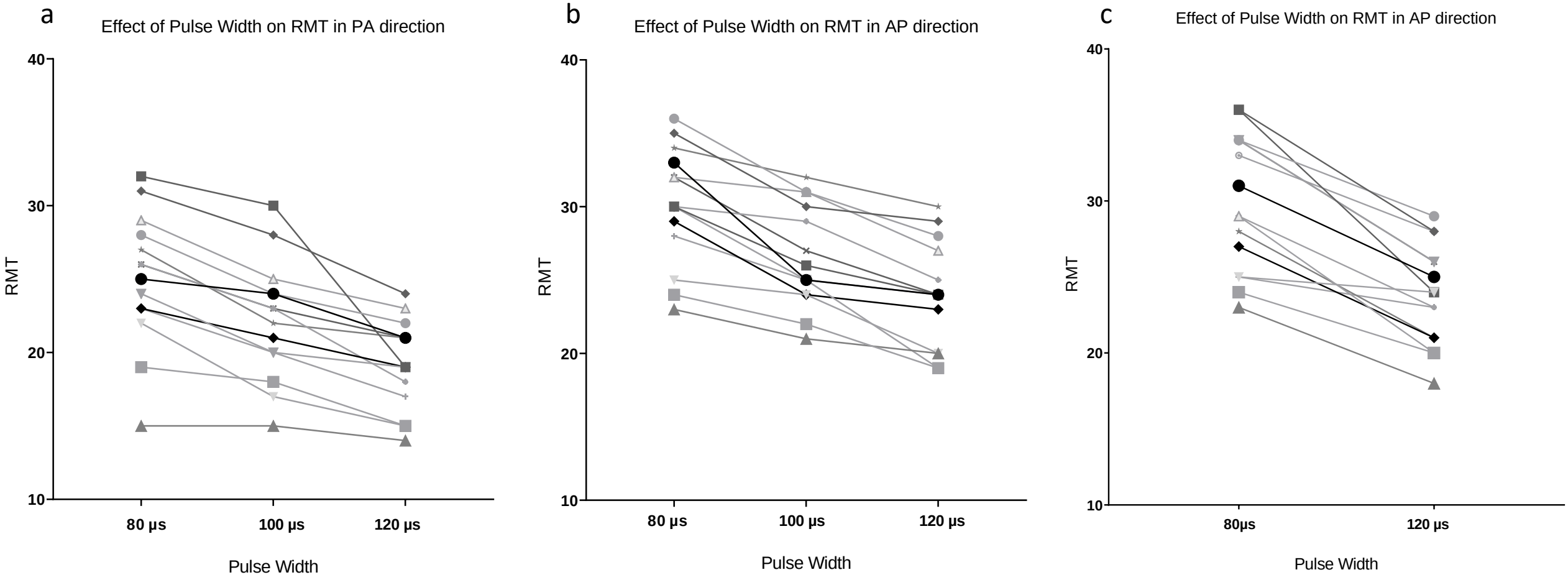

90% RMT at 5 Hz with cTMS with selected pulse shapes.
1mv at 0.2 Hz with Magstim
2 baseline measurements **25** pulses
6 trains of **200** pulses at **5 Hz**; with **15** pulse in-between measurements
Post measurement: 7 measurements with **25** pulses at the start of every 5 minutes.
BL1
BL2
1
2
3
4
5
0min
5min
10min
15min
20min
25min
30min

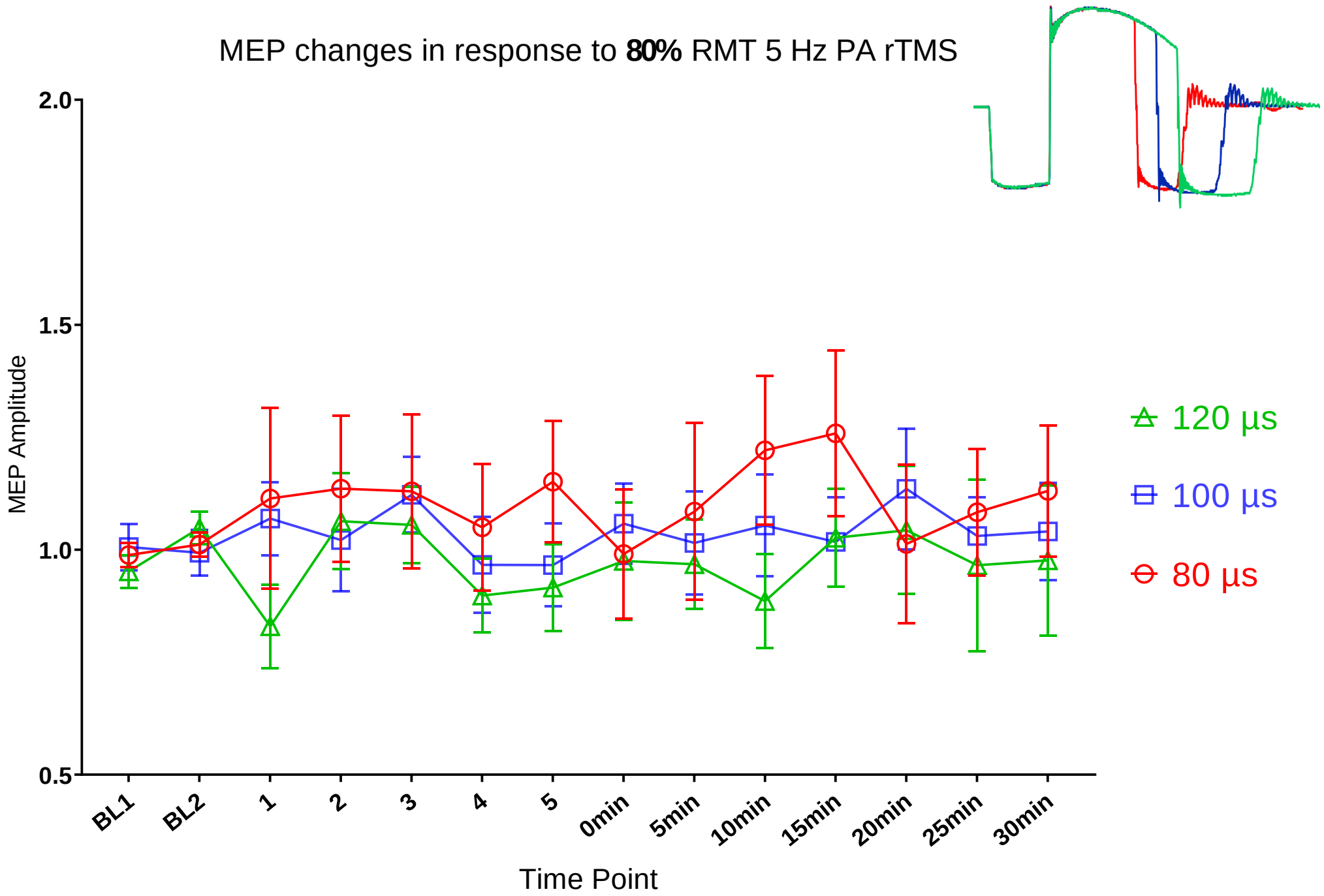
A

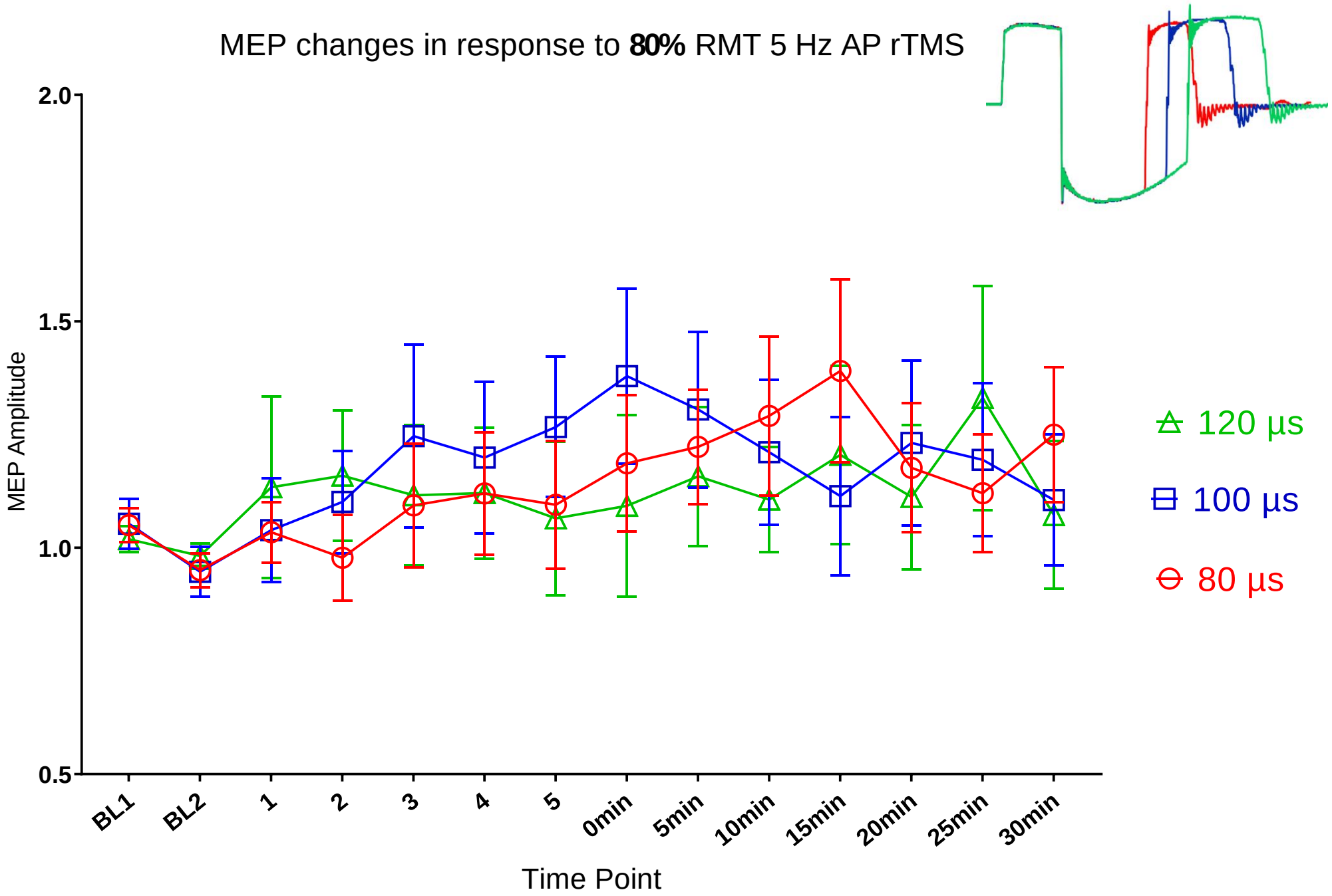


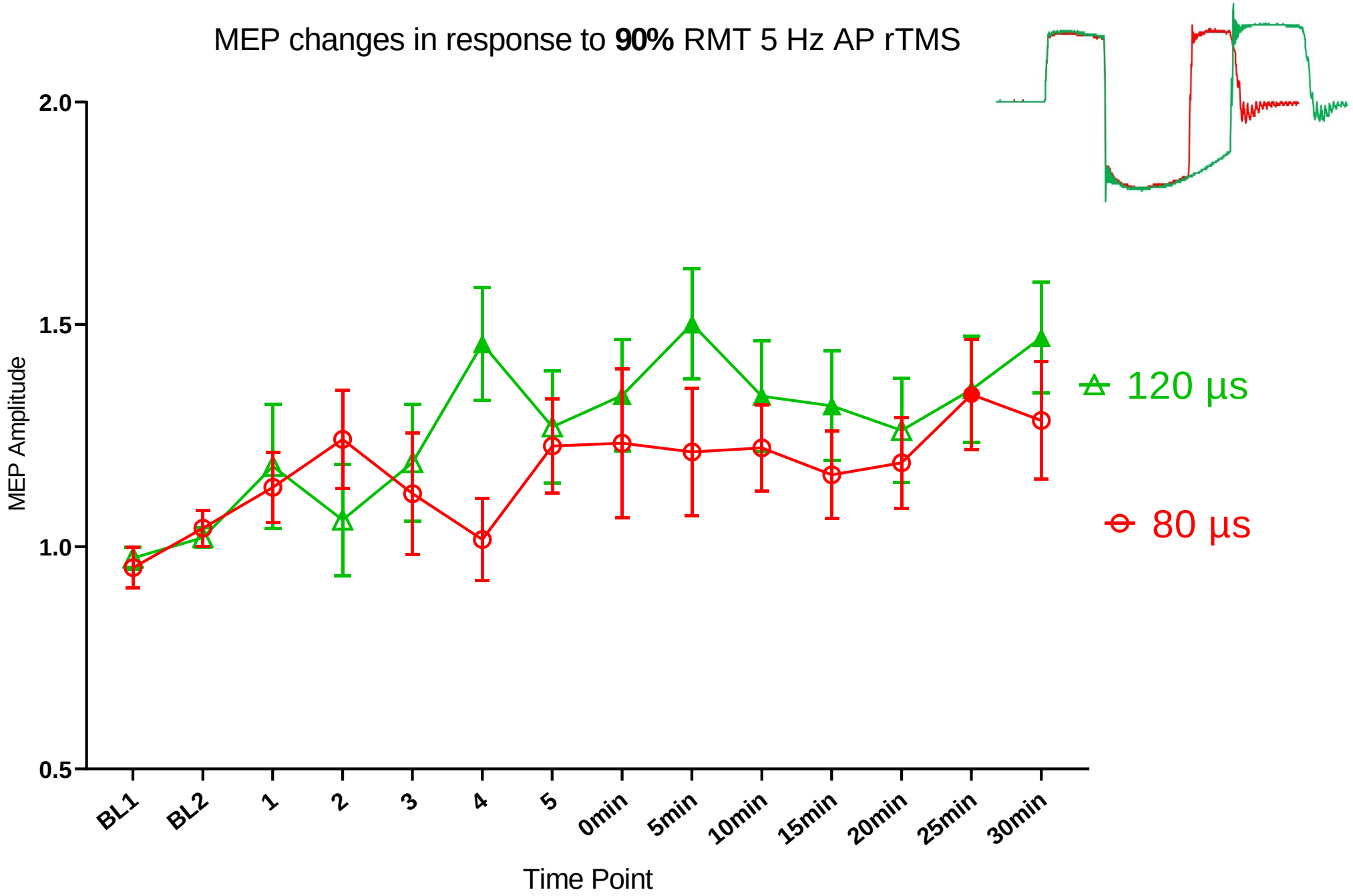
B




a
Effect of Pulse Width on RMT in PA direction
RMT
40
30
20
10
80 µs
100 µs
120 µs
Pulse Width
b
Effect of Pulse Width on RMT in AP direction
RMT
40
30
20
10
80 µs
100 µs
120 µs
Pulse Width
c
Effect of Pulse Width on RMT in AP direction
RMT
40
30
20
10
80µs
120 µs
Pulse Width


MEP changes in response to **80%** RMT 5 Hz PA rTMS
MEP Amplitude
2.0
1.5
1.0
0.5
BL1
BL2
1
2
3
4
5
0min
5min
10min
15min
20min
25min
30min
Time Point
120 µs
100 µs
80 µs


MEP changes in response to **80%** RMT 5 Hz AP rTMS
2.0
1.5
1.0
0.5
MEP Amplitude
BL1
BL2
1
2
3
4
5
0min
5min
10min
15min
20min
25min
30min
Time Point
120 µs
100 µs
80 µs


MEP changes in response to **90%** RMT 5 Hz AP rTMS
2.0
1.5
1.0
0.5
MEP Amplitude
BL1
BL2
1
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4
5
0min
5min
10min
15min
20min
25min
30min
Time Point
120 µs
80 µs