Increasing pulse widths and intensity increase the efficacy of high frequency rTMS in inducing excitatory aftereffects.

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Abstract:

Introduction: High frequency repetitive transcranial magnetic stimulation induces excitation (i.e. post-stimulation increase of motor evoked potential (MEP) amplitudes) when applied to the motor cortex. The effects differ according to pulse width, probably by selectively stimulating distinct segments of neurons due to their different membrane properties. Here we focus on the aftereffects generated with high frequency controllable pulse TMS (cTMS).

Objectives: To investigate the influence of different stimulation intensities, pulse widths and direction on the excitatory plastic aftereffects of high frequency (HF) rTMS 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 applying 1200 bidirectional pulses with the main component widths of 80 and 120 microseconds. 80% resting motor threshold (RMT) intensity was investigated for both anterior-posterior (AP) and posterior-anterior (PA), and in a second experiment at 90% RMT in the AP direction.

Results: 80% HF rTMS did not produce any significant excitation in either AP or PA direction. 90% RMT AP stimulation with 120 microsecond-wide pulses induced more significant excitatory aftereffect, when compared to the 80 microsecond-wide pulses.

Conclusions: HF rTMS with wider pulses is more effective in producing excitatory aftereffects, which 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 the treatment of depression and chronic pain (Lefaucheur et al., 2014). More efficacious protocols are needed and are the subject of two ongoing NIH research initiatives. The key rTMS parameters involved in its efficacy, stimulation frequency and intensity, and number of pulses and sessions have been closely investigated (Rossini et al., 2015). However, there are few studies on the impact of pulse width on rTMS outcome because of the scarcity of devices with adjustable pulse widths. However, we now have the technology that allows us to change pulse widths as easily as changing frequency and stimulation patterns (Peterchev et al., 2011).

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

In this study, we explored the interplay of coil orientation, pulse width, and pulse intensity on the aftereffects of a 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. Sessions were randomized and with at least one week gaps to avoid possible carry over effects.

***Methods*:**

Participants

For the first experiment, we recruited fourteen subjects, four males and ten females, mean age 23.5 ± 2.6 SD years. For the second experiment, a different set of fifteen healthy volunteers was recruited, four males and eleven females, mean age 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. With this device and using the standard coil for the wider pulse shapes intensities above 50% of maximal stimulator output (MSO) were not possible, a resting motor threshold (RMT) 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 digitally for offline analysis. The peak-to-peak MEP amplitude served as an index for M1 excitability. The participants were requested to relax the right FDI during the measurements. Individual traces contaminated by voluntary muscle contraction before the TMS pulse(s) 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 representation.

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

Step 1: Determining thresholds and baseline:

For each session, we use the Magstim 200^2 with the D70 coil to determine the RMT and the MSO intensity that gave a resonse of approximately 1 mV for the baseline measurement intensity in the PA direction. In addition, we determined RMT for the cTMS pulse shape being used for the intervention, both for the PA and the AP direction (coil rotated by 180 degrees), as a reference for the 5 Hz rTMS stimulation. The baseline measurements consisted of two 25-pulse measurements at 0.25 Hz with the previously determined MSO intensity giving a 1 mV response.

Step 2: The interventional cTMS stimulation:

In order to isolate the effect of altering the pulse width without interference from the directionality of the individual pulses, we used custom, balanced bidirectional pulse shapes which are easier to fire at higher frequencies (Peterchev et al., 2011). We used three widths of the main component (80µs, 100µs, and 120µs) in the PA and the AP direction as shown in Fig 2. We used 80% of the appropriate RMT for the rTMS in the corresponding direction. For the second experiment, we used 90% RMT with 80 and 120µs pulse shapes for the 5 Hz rTMS only in the AP direction.

We triggered the cTMS device at 5Hz using an external trigger to fire the customized pulse shapes. For the first experiment we applied 1200 pulse of rTMS in both the AP and the PA direction at 5 Hz with 80% RMT intensity in 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 in the antero-posterior (AP) direction, which is more effective with 5Hz rTMS (Sommer et al., 2013).

Step 3: After the final rTMS pulse block, we recorded 25 pulses with the baseline MSO intensity for 1mA response every five minutes for 30 minutes using Magstim 200[2].

Figure 2: Pulse shapes detected 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 time 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, using the Bonferroni-Dunn method to correct for multiple comparisons.

***Results*:**

RMT: For the first experiment longer pulse shapes had significantly lower RMTs than shorter pulse shapes in the PA direction () and the AP direction (Fig 3.a and 3.b, respectively; $p < 0.0001$ for both). 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: 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 significant effects 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 effects outlasting the stimulation, and there was no significant effect of changing the pulse widths ($p>0.1$; Fig.4). For AP-directed stimulation, there was no significant change over time ($p =0.4769$, $F=0.9530$) and no significant shift from the baseline for any time point ($p >0.2$; Fig.5), but there was a significant effect of pulse width change with ($p<0.001$; $F=12.76$). Additionally, AP-directed stimulation produced significantly greater excitation than PA-directed stimulation ($p<0.05$; $F= 0.9826$). Post-hoc, multiple paired t-tests showed no significant difference across all time points. No significant difference was found in the baseline measurements.

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

For the second experiment, two-way ANOVA revealed significant effects for pulse widths ($p=0.0278$; $F= 4.876$) and change over time ($p=0.0135$; $F=2.098$). Post-hoc t-tests showed that the 120 µs pulse shape produced significant excitation at six time points (corrected $p <0.009$, paired two-tailed t-test) compared to the 80µs pulses, which only exhibited significant excitation at one time point (corrected $p= 0.02$, paired two-tailed t-test; Fig.5). No significant difference was found in 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 showed that prolonging the pulse duration of HF rTMS led to significant excitation for 90% RMT 5 Hz AP rTMS. Although there were no significant aftereffects after 80% RMT 5 Hz rTMS with pulse widths of 80, 100 and 120µs in either direction, we found that AP stimulation is more sensitive to pulse width change ($p <0.001$) and more effective in producing plastic aftereffects than PA stimulation ($p<0.05$). This has been demonstrated in many rTMS protocols especially for 5 Hz rTMS (Rothkegel et al., 2010; Sommer et al., 2013).

Only the AP-directed stimulation was used with the 90% RMT employing the longest (120µs) and shortest (80µs) pulse shapes. Again, we reproduced the excitatory effects of bidirectional AP pulses when using an interval design (Rothkegel et al., 2010). However, the key finding is that the 120 µs pulses with 5 Hz rTMS increased cortical excitability more than the 80µs pulses.

In all subjects, RMT (Fig 3) decreased with increasing pulse width in agreement with previous reports (D'Ostilio et al., 2016). While the thresholds as percentage of the device's MSO decreased, this apparent decrease in the threshold is not actually correct. The read-out amplitude does not reflect the total energy of the pulse, which is a function of the area of the pulse shape and not just the stimulation intensity. Wider pulses require more energy to elicit responses in the cortex (Barker et al., 1991; Peterchev et al., 2013; Grill, 2015). The higher total pulse energy could explain the seemingly greater efficacy of wider pulses when only pulse amplitude is considered (Modugno et al., 2001). Using pulse width as an analogue for intensity, high frequency stimulation of rabbit cortex required pulses longer than 100µs to significantly potentiate neurons (McNaughton et al., 1978). However, pulse width and intensity work through different mechanism, since increasing the pulse width of 1 Hz rTMS above 100µs changed the inhibitory outcome into an excitatory one (Halawa et al., 2019), which is contrary to the conventional observation that increasing the stimulation intensity in 1 Hz rTMS 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 pulses shorter than 100µs are usually unable to stimulate smaller

dendrites, even using exceedingly high amplitudes, while the axon and soma are still responsive for pulses as short as 10µs (Rattay et al., 2012). Because dendrites lack myelin (Aberra et al., 2018) and have a small diameter (Pashut et al., 2011), they respond preferentially to wider pulses. That could imply 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 with higher amplitudes and for a longer period after stimulation ceases (Lee and Fried, 2017), which shows that dendrites have a greater plasticity than axons. A similar effect was shown in single neurons where current injection into dendrites furthest from the soma produced longer and larger action potentials compared to somatic current injection (Larkum et al., 2007), especially in response to higher frequency and longer pulse width stimulation (Ledergerber and Larkum, 2010).

Those special plastic properties could be mediated by their high resistance spines which allow them to passively amplify local synaptic depolarization up to 50-fold, where the higher spine neck resistance leads 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 effective in producing cooperativity mediated LTP compared to proximal dendrite stimulation (Weber et al., 2016).

The significance of dendritic stimulation in producing lasting plastic aftereffects through LTP in response to rTMS is emphasized (Sjöström et al., 2008; Müller-Dahlhaus and Vlachos, 2013). In this study we showed that increasing the pulse width increased the excitatory efficacy of HF rTMS. This is probably due to a stronger dendritic activation, resulting from their unique membrane properties and their important role in inducing synaptic plasticity.

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Declaration of interest:

None declared.

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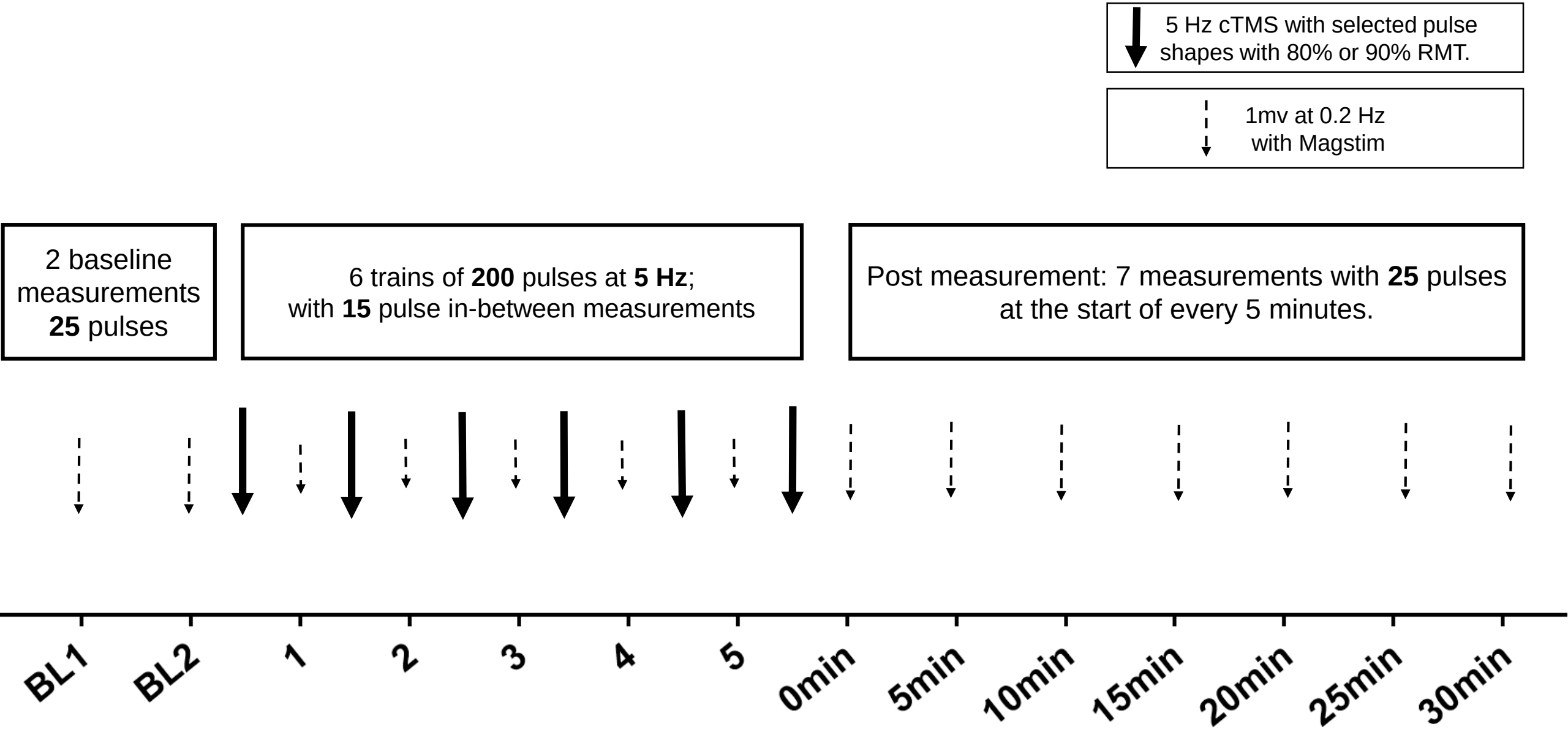
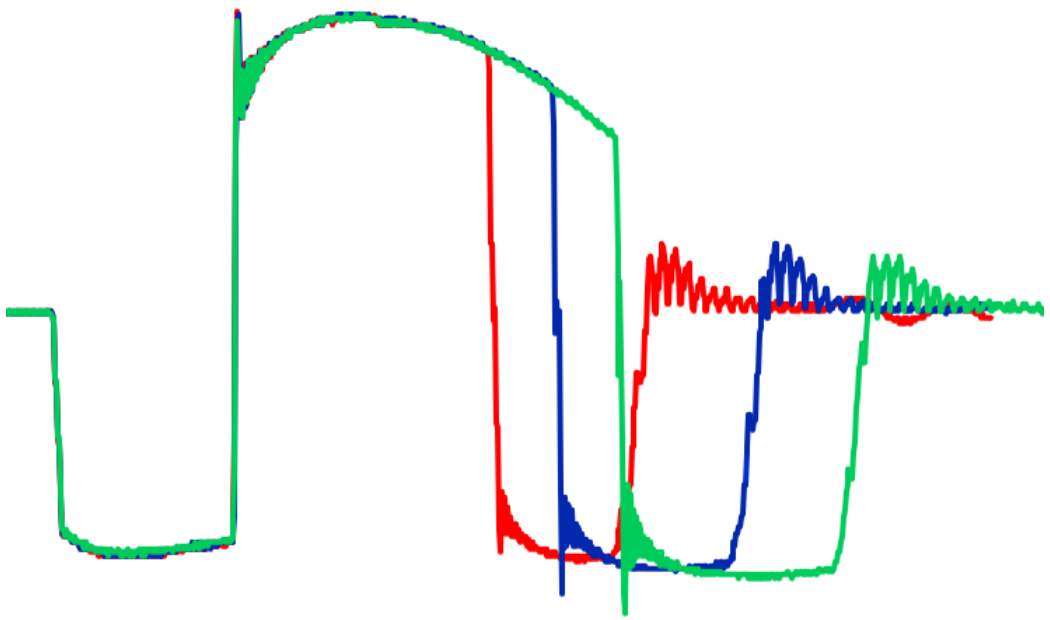
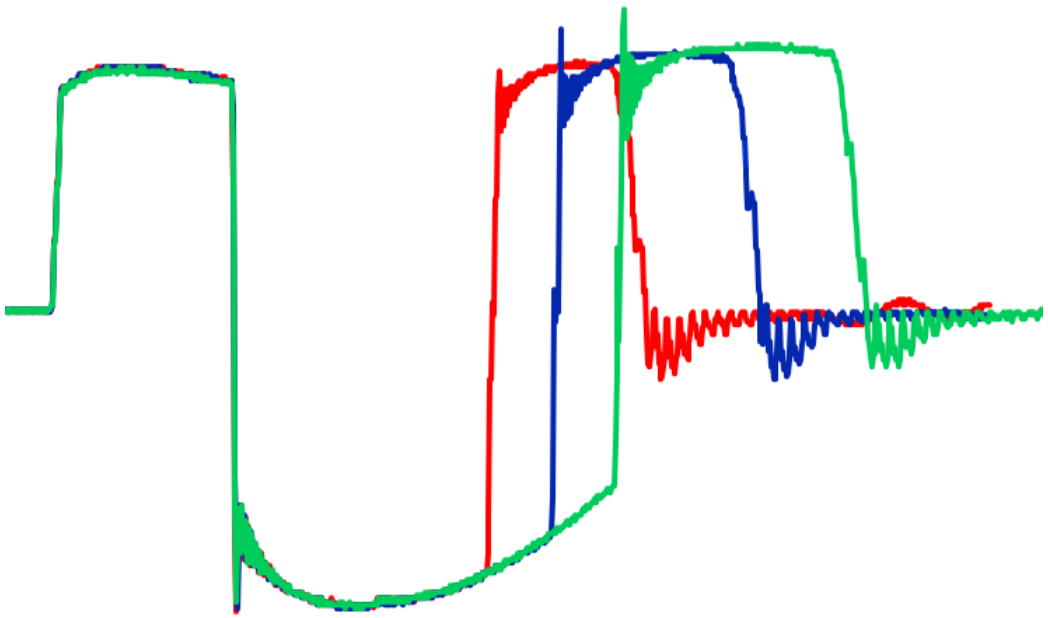
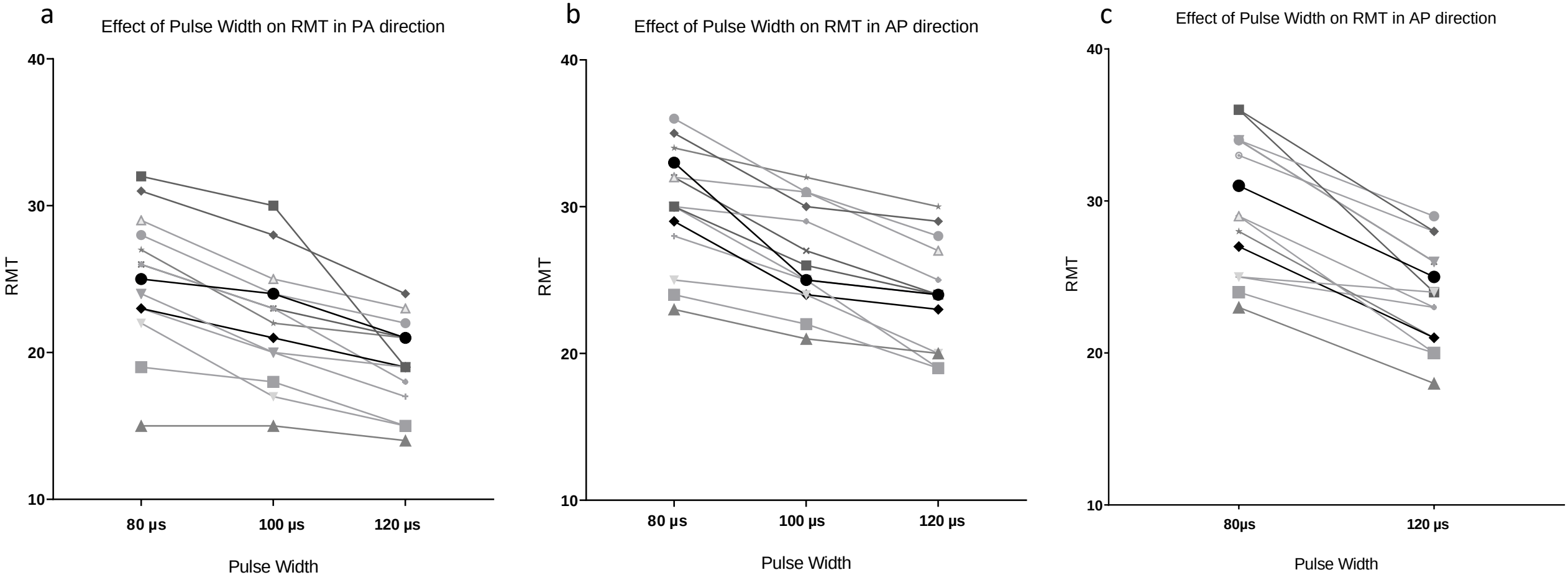

5 Hz cTMS with selected pulse shapes with 80% or 90% RMT.
1mv at 0.2 Hz with Magstim
2 baseline measurements **25** pulses
6 trains of **200** pulses at **5 Hz**; with **15** pulse in-between measurements
Post measurement: 7 measurements with **25** pulses at the start of every 5 minutes.
BL1
BL2
1
2
3
4
5
0min
5min
10min
15min
20min
25min
30min

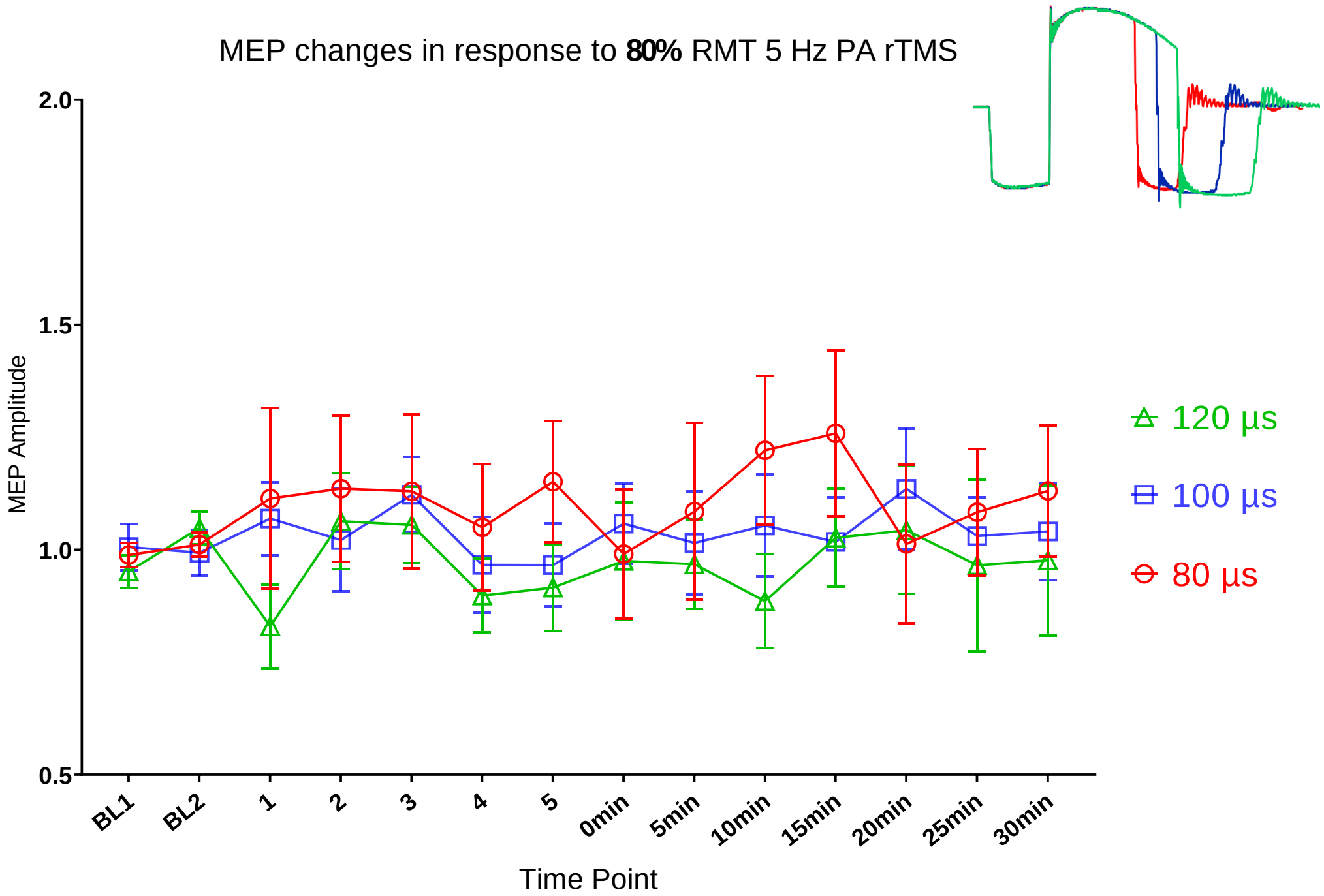
A



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
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BL1
BL2
1
2
3
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5
0min
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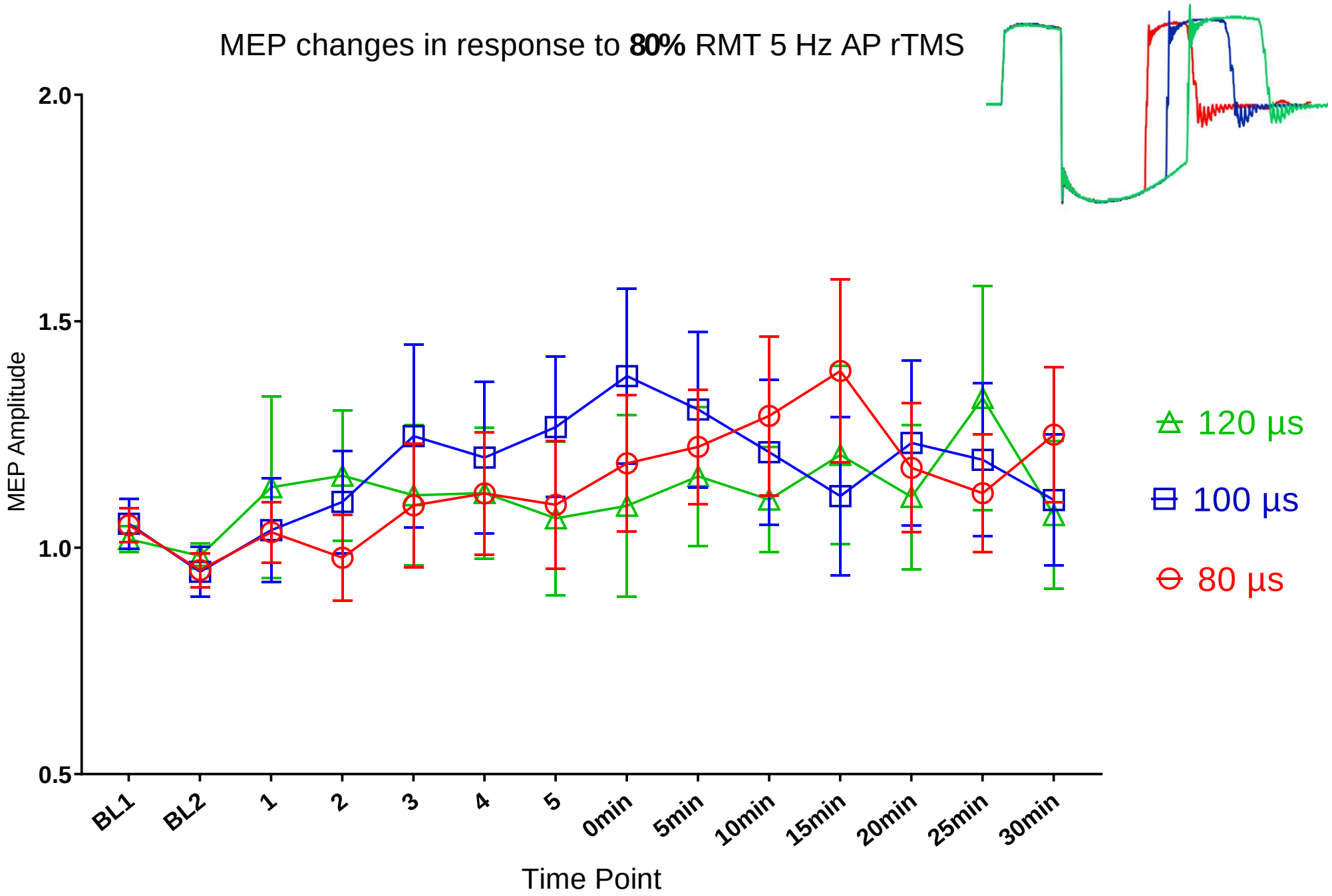
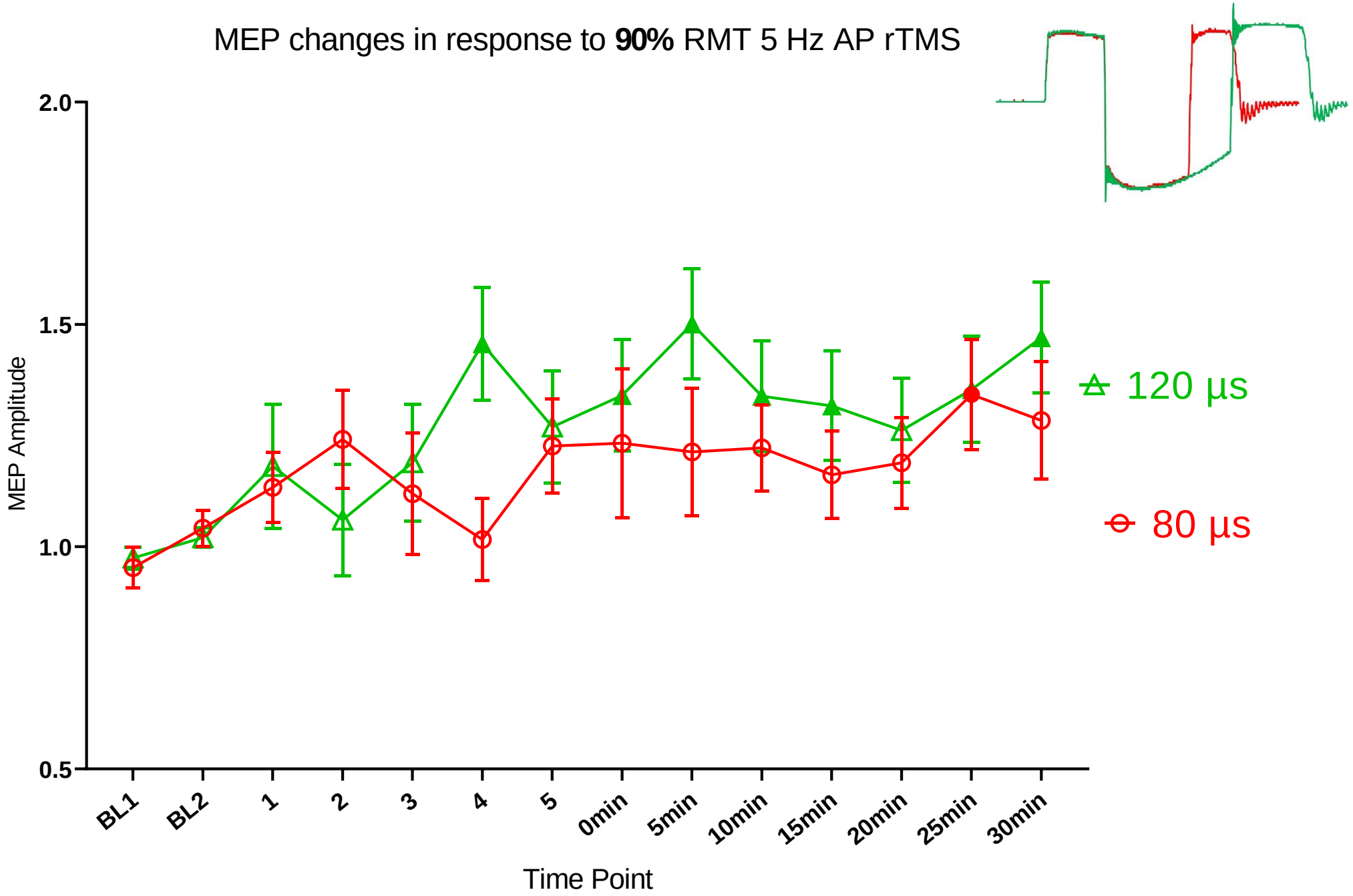
10min
15min
20min
25min
30min
Time Point
120 µs
100 µs
80 µs


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
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1
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10min
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25min
30min
Time Point
120 µs
80 µs