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Half sine, monophasic and biphasic transcranial magnetic stimulation of the human motor cortex

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Abstract

Objective: To compare half sine transcranial magnetic stimuli (TMS) with conventional monophasic and biphasic stimuli, measuring resting and active motor threshold, motor evoked potential (MEP) input/output curve, MEP latency, and silent period duration.

Methods: We stimulated the dominant hand representation of the motor cortex in 12 healthy subjects utilising two different MagPro stimulators to generate TMS pulses of distinct monophasic, half sine and biphasic shape with anteriorly or posteriorly directed current flow.

Results: The markedly asymmetric monophasic pulse with a posterior current flow in the brain yielded a higher motor threshold, a less steep MEP input/output curve and a longer latency than all other TMS types. Similar but less pronounced results were obtained with a less asymmetric half sine pulses. The biphasic stimuli yielded the lowest motor threshold and a short latency, particularly with the posterior current direction.

Conclusions: The more asymmetric the monophasic pulse, the stronger the difference to biphasic pulses. The 3rd and 4th quarter cycle of the biphasic waveform make it longer than any other waveform studied here and likely contribute to lowering motor threshold, shortening MEP latency and reversing the influence of current direction.

Significance: This systematic comparison of 3 waveforms and two current directions allows a better understanding of the mechanisms of TMS.

Keywords: Transcranial magnetic stimulation; Stimulus configuration; Monophasic; Biphasic; Motor cortex

1. Introduction

The difference between biphasic and monophasic transcranial magnetic stimulation (TMS) is increasingly noticed (Corthout et al., 2001; Kammer et al., 2001; Niehaus et al., 2000) and taken into account also in the field of repetitive TMS (rTMS) (Arai et al., 2005; Sommer et al., 2002; Tings et al., 2005). The exact reason for differences, e.g. with regard to motor threshold is still debated, so is the role of the different components of a biphasic pulse in vivo and in vitro (Kammer et al., 2001; Maccabee et al., 1998).

The half sine pulse provided by the MagPro X100 MagOption stimulator (Medtronic Inc., Minneapolis, MN, USA) is identical to the biphasic pulse of that machine, but cut after the second quarter cycle. For the monophasic waveform, the second quarter cycle is cut earlier and then gradually tapers off and therefore differs markedly from the second quarter cycle of the biphasic pulse. For comparison, note that the Magstim 200 stimulator (The Magstim Company, Whitland, Dyfed, UK) generates a monophasic pulse, and the Magstim Rapid and Rapid^2 stimulator generate biphasic pulses (Fig. 1).

We were curious to learn whether the half sine waveform, being in between the monophasic and the biphasic waveform, gives any insight about the role of the

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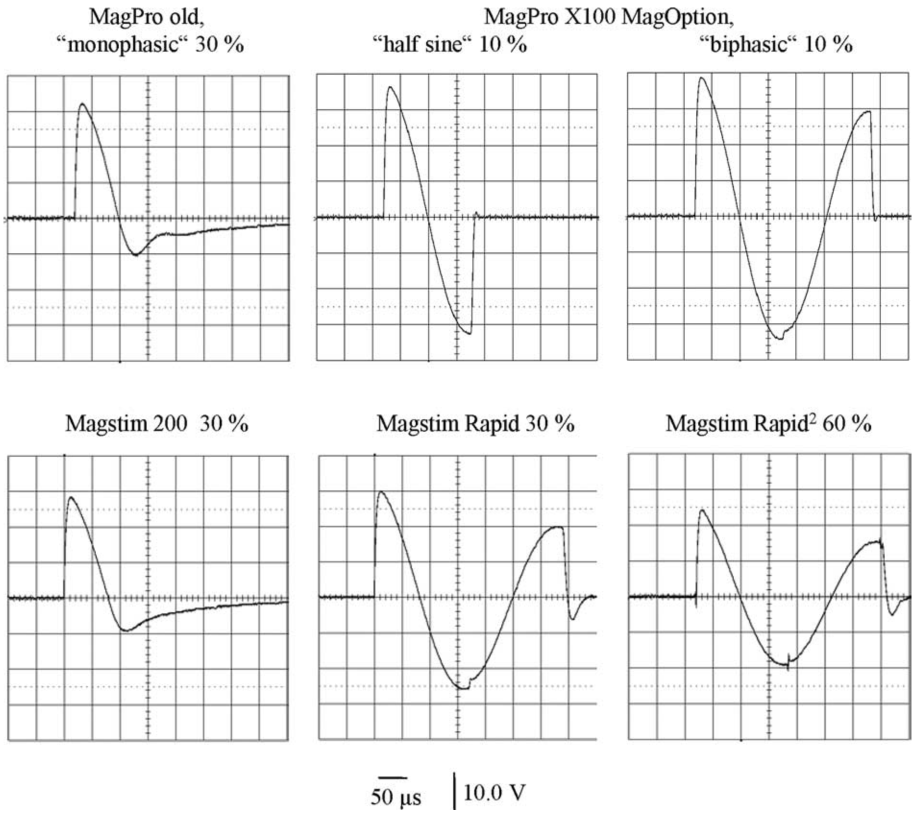

Fig. 1. Current induced in a probe coil of 1 cm diameter by different types of transcranial magnetic stimulators, recorded and stored by an oscilloscope (LeCroy 9350C, Chestnut Ridge, NY, USA). Stimulus intensity as annotated in percent of maximum stimulator output. Upper part, waveforms studied in this manuscript. Upper left, waveform induced by the old (green) MagPro stimulator in the ‘monophasic’ mode. Upper middle and upper right, waveforms induced by the MagPro X100 MagOption in the ‘half sine’ mode (upper middle) and in the ‘biphasic’ mode (upper right). For all upper graphs, the same Dantec MC-B70 coil was used. Lower part, other waveforms induced by different Magstim stimulators recorded with the same set-up and illustrated for comparison. Identical ENG SP2 8606 figure-8-coil for Magstim 200 and Magstim Rapid; P/N 3110 00 S/N074 figure-8-coil for Magstim Rapid^2.

TMS waveform with regard to typical measures of corticospinal excitability such as motor threshold, motor evoked potential (MEP) latency, MEP input/output curve and silent period duration, and therefore compared all 3 types of pulses in the same group of subjects. We could not study other measures such as short-interval (Kujirai et al., 1993; Ziemann et al., 1996) or long-interval intracortical inhibition (Chen, 2004) because of technical limitations to the monophasic pulse repetition rate.

2. Material and methods

All measures were studied in 12 healthy subjects (mean age 27.5, range 22–35 years, 6 women) with no previous or current medical or neurological disease and no intake of medication except for oral contraceptives in two of the 6 women. In all subjects we studied the dominant hand, stimulating the contralateral motor cortex. Eleven of 12 subjects were right-handed with a mean Olfield 10-items handedness score of 87.9 ± 18.6 of 100 points of right-handedness (mean ± SD) (Oldfield, 1971). The experiments were approved by the ethics committee of the University of Göttingen. For all experiments we used the same slightly bent figure-of-8 coil (MC B70, Dantec S.A., Skovlunde, Denmark) either with the old, green MagPro stimulator (old version, produced earlier than 2003) or a new, white MagPro X 100 MagOption stimulator (produced from 2003 on).

2.1. Six types of TMS

During the preparation of this project it turned out that the MagPro X100 MagOption stimulator used in our lab was not able to produce a truly monophasic pulse, but produced a half sine pulse instead even when waveform switch was set at monophasic. Therefore, we had to use the monophasic pulse from the old MagPro stimulator (Dantec S.A., Skovlunde, Denmark).

During the review process of this manuscript, one anonymous reviewer indicated that the MagPro X100 MagOption used in his/her laboratory is able to generate all 4 types of waveforms correctly (monophasic, half sine, biphasic, biphasic burst). We therefore had the machine used in our lab tested by the manufacturer, who replaced a faulty monophasic clamp diode. After repair, the MagPro X100 MagOption we are using is able to generate all 4 types of waveforms correctly. However, for the data presented here and generated before the repair, we had to use the old MagPro to generate truly monophasic pulses.

To investigate 6 types of TMS (old MagPro monophasic anteriorly directed stimuli, old MagPro monophasic posteriorly directed stimuli, half sine anteriorly and posteriorly directed stimuli from the MagPro X100 MagOption stimulator, and biphasic anteriorly and posteriorly directed stimuli from the MagPro X100 MagOption stimulator), the subjects were studied in 3 separate sessions using two kind of pulse waveforms in each one. The order of pulse waveforms was randomized for each volunteer, and subjects were not told any details about the TMS types. Experiments took place at least half an hour apart from each other. In this manuscript the current direction is always indicated as the initial current flow in the brain, which is opposite to the current direction in the coil (Bohning, 2000).

2.2. Motor threshold

In each experimental session, we first determined the optimal dominant abductor digiti minimi (ADM) motor representation, since it is not necessarily identical for all types of TMS, and marked the respective spot with a pen on the skin. We determined the resting motor threshold (RMT), i.e. the lowest intensity that yielded motor evoked potentials (MEPs) of >50 μV from the muscle at rest in at least 5 of 10 consecutive trials, and the active resting threshold (AMT), i.e. the lowest intensity that yielded motor evoked potentials of >250 μV from the tonically contracted muscle in at least 5 out of 10 consecutive trials (Rothwell et al., 1999). Step width for threshold determination was about 1% of stimulator output. For ADM electromyography we used silver–silverchloride electrodes in a belly-tendon montage. For recording we used the ‘Signal’ software and a CED 1401 hardware (Cambridge Electronic Design, Cambridge, UK) at a sampling rate of 10,000 Hz and filtered at 1.6 Hz and 1 kHz. For analysis we calculated a repeated-measures ANOVA with *threshold* (RMT, AMT), *waveform* (mono, half sine, bi) and *current direction* (anterior, posterior) as within-subjects factors. Post-hoc *t* tests were paired and two-tailed. Similar follow-up ANOVAS were calculated separately comparing monophasic and half sine as well as half sine and biphasic pulses.

2.3. MEP I–O curve; MEP latency

For studying the MEP I–O curve, we applied 10 stimuli each for the intensity of RMT $+10$ A/μs, and RMT $+20$ A/μs. We did not use intensity steps relative to the threshold, since this would have resulted in unequal step widths for the different types of TMS. We normalized the raw values to the maximal M-wave amplitude determined by supramaximal peripheral stimulation using a conventional EMG stimulation block and an electrical stimulator (Multipulse Stimulator model D 185, Digitimer Inc., Welwyn Garden City, UK). For analysis we used a repeated-measures ANOVAs with *intensity* (3 levels), *waveform* (3 levels) and *current direction* (two levels) as within-subjects factors. Post-hoc *t* tests were paired and two-tailed. Similar follow-up ANOVAS were calculated separately comparing monophasic and half sine as well as half sine and biphasic pulses.

In addition, we measured the mean MEP onset latency from the 10 trials with RMT $+20$ A/μs intensity in each subject and calculated a factorial ANOVA with *pulse type* (6 levels) as between-subjects factor. Post-hoc *t* tests were paired and two-tailed. Similar follow-up ANOVAS were calculated separately comparing monophasic and half sine as well as half sine and biphasic pulses.

2.4. Silent period

We recorded the contralateral silent period (cSP) while the subjects abducted the small finger of the investigated hand at about 20% maximum voluntary contraction, monitored by acoustic and visual feedback (Myograph II, Toennies GmbH, Freiburg, Germany). We used 10 pulses each at RMT $+10$ A/μs, RMT $+20$ A/μs and RMT $+25$ A/μs. In each trial the cSP duration was measured off-line from the onset of the MEP to the reoccurrence of any sustained EMG activity (Orth and Rothwell, 2004). For analysis we calculated a repeated-measures ANOVA with *intensity* (3 levels), *waveform* (3 levels) and *current direction* (two levels) as within-subjects factors. Post-hoc *t* tests were paired and two-tailed and calculated on the pooled values of all intensity levels. Similar follow-up ANOVAS were calculated separately comparing monophasic and half sine as well as half sine and biphasic pulses.

3. Results

3.1. Side effects

No side effects of TMS were reported.

3.2. Motor threshold

The motor threshold was differentiated according to the type of stimulation and the current direction (Fig. 2). It was generally higher with monophasic than with half sine or biphasic pulses. For monophasic and half sine stimulation, the posteriorly oriented pulses yielded a higher motor threshold than the anteriorly oriented currents, the difference being most pronounced for the monophasic configuration. By contrast, for biphasic stimulation posteriorly oriented stimuli yielded lower thresholds than anteriorly oriented ones (repeated-measures ANOVA, effect of threshold (RMT vs. AMT), $F(1,11)=104.5$, $P<0.0001$; effect of waveform, $F(2,22)=107.8$, $P<0.0001$; no effect of current direction; interaction of threshold by waveform,

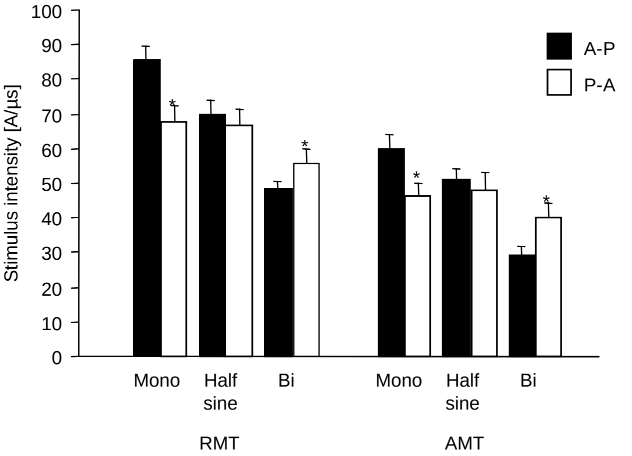

Fig. 2. Motor threshold with the target muscle at rest (RMT) or during voluntary target muscle contraction (AMT), shown for the 6 types of TMS studied, mean ± SE. Asterisks indicate significant post-hoc differences between current directions for a particular waveform.

$F(2,22) = 7.3$, $P = 0.0037$; interaction of waveform by current direction, $F(2,22) = 52.6$, $P < 0.0001$). Post-hoc *t* tests yielded a significant difference between all waveforms.

Follow-up ANOVAs yielded a difference between monophasic and half sine pulses (repeated-measures ANOVA, effect of threshold, $F(1,11) = 118.6$, $P < 0.0001$; effect of waveform, $F(1,11) = 23.9$, $P = 0.0005$, effect of current direction, $F(1,11) = 17.3$, $P = 0.002$; interaction of waveform by current direction, $F(1,11) = 23.1$, $P = 0.0005$; interaction of threshold by waveform, $F(1,11) = 4.8$, $P = 0.052$) as well as between half sine and biphasic pulses (repeated-measures ANOVA, effect of threshold, $F(1,11) = 129.8$, $P < 0.0001$; effect of waveform, $F(1,11) = 90.9$, $P < 0.0001$, effect of current direction, $P = 0.18$; interaction of waveform by current direction, $F(1,11) = 37.9$, $P < 0.0001$, no other interaction).

3.3. MEP latency

The MEP latency was significantly different between waveforms. The pattern resembled that of the motor threshold (Fig. 3), with longer latencies for the posteriorly oriented pulses, particularly in the case of monophasic pulses, and again a reversed situation for the biphasic waveform where anteriorly oriented pulses yielded slightly longer latencies (repeated-measures ANOVA, effect of waveform, $F(2,22) = 19.3$, $P < 0.0001$; effect of current direction, $F(1,11) = 14.9$, $P = 0.003$; interaction of waveform by current direction, $F(2,22) = 15.1$, $P < 0.0001$). Post-hoc *t* tests yielded a significant difference between monophasic and half sine waveforms as well as between the monophasic and the biphasic waveforms.

Follow-up ANOVAs yielded a difference between monophasic and half sine stimuli (repeated-measures ANOVA, effect of waveform, $F(1,11) = 23.0$, $P = 0.0006$, effect of current direction, $F(1,11) = 30.7$, $P < 0.0001$; interaction of waveform by current direction, $F(1,11) = 10.2$, $P = 0.009$), but not between half sine and biphasic pulses (repeated-measures ANOVA, effect of waveform, $F(1,11) = 4.4$, $P = 0.059$, effect of current direction, $P = 0.95$; no interaction).

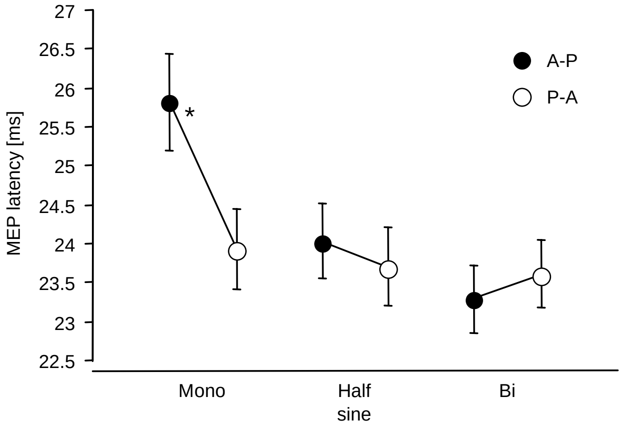

Fig. 3. Motor evoked potential latency (ms), mean ± SE. Asterisks indicate significant post-hoc differences between current directions for a particular waveform.

3.4. MEP I–O curve

The increase of MEP amplitude with rising stimulus intensity was least steep with the monophasic posteriorly oriented pulses (repeated-measures ANOVA, effect of intensity, $F(2,22) = 35.6$, $P < 0.0001$; no main effect of waveform or current direction; interaction of intensity by waveform, $F(4,44) = 3.67$, $P = 0.011$; Fig. 4). Post-hoc tests yielded a significant difference between the posteriorly oriented currents of the monophasic type and the half sine as well as the biphasic pulse.

Follow-up ANOVAs yielded a difference between monophasic and half sine pulses (repeated-measures ANOVA, effect of intensity, $F(2,22) = 30.2$, $P < 0.0001$; effect of waveform, $F(1,11) = 3.9$, $P = 0.071$, effect of

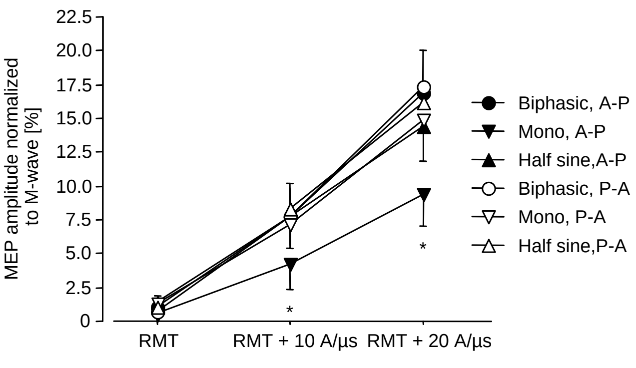

Fig. 4. MEP amplitude input/output curves tested with fixed step widths; mean ± SE. Asterisks indicate significant differences in post-hoc *t* tests.

current direction, $F(1,11)=5.0$, $P=0.046$; interaction of intensity by waveform, $F(2,22)=2.7$, $P=0.09$; interaction of intensity by current direction, $F(2,22)=3.6$, $P=0.044$, no other interaction), but not between half sine and biphasic pulses (repeated-measures ANOVA, effect of intensity, $F(2,22)=40.8$, $P<0.0001$; no effect of waveform, $P=0.7$; no effect of current direction, no significant interaction).

3.5. Silent period

The contralateral silent period duration was shortest with the monophasic pulses, intermediate with half sine pulses, and longest with the biphasic pulses. For monophasic and half sine pulses the posteriorly oriented currents yielded a slightly longer SP duration than the anteriorly oriented pulses, the reverse was true for the biphasic pulses (Fig. 5). A repeated-measures ANOVA yielded an effect of intensity, $F(2,22)=59.7$, $P<0.0001$; an effect of waveform, $F(2,22)=14.6$, $P<0.0001$; no effect of current direction, and no significant interaction. Post-hoc tests yielded a significant difference between all waveforms and between all levels of intensity.

Follow-up ANOVAs yielded a difference between monophasic and half sine pulses (repeated-measures ANOVA, effect of intensity, $F(2,22)=63.9$, $P<0.0001$; effect of waveform, $F(1,11)=8.7$, $P=0.013$, effect of current direction, $P=0.34$; no significant interaction), and in particular between half sine and biphasic pulses (repeated-measures ANOVA, effect of intensity, $F(2,22)=42.2$, $P<0.0001$; effect of waveform, $F(1,11)=5.8$, $P=0.035$, effect of current direction, $P=0.89$; interaction of intensity by waveform, $F(2,22)=6.4$, $P=0.006$, interaction of intensity by current direction, $F(2,22)=2.7$, $P=0.087$; interaction of waveform by current direction, $F(1,11)=4.3$, $P=0.061$; no other interaction).

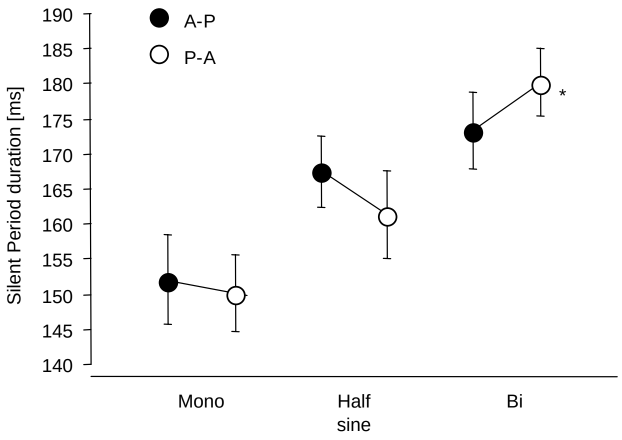

Fig. 5. Contralateral silent period duration with 3 levels of stimulus intensities pooled; mean ± SE. Asterisks indicate significant post-hoc differences between current directions for a particular waveform.

4. Discussion

This study expands earlier data (Kammer et al., 2001; Niehaus et al., 2000) by showing that when probing measures of corticospinal excitability with single pulse TMS the half sine pulses of the new MagPro TMS stimulator yield results in between those of the monophasic pulses and the biphasic configuration. This holds true for motor threshold, MEP latency and SP duration. Our data also show that the influence of the current direction is of the same type for the monophasic and the half sine pulse, though more pronounced for the first than the latter, but reversed for the biphasic waveform.

The MEP latency difference is consistent with findings of earlier reports (Day et al., 1989; Di Lazzaro et al., 2001; Sakai et al., 1997). It has been suggested that either different structures might be activated by different waveforms and current directions, or that the same sets of interneurons in the motor cortex are activated at different sites (Di Lazzaro et al., 2001; Kammer et al., 2001). This assumption was based on epidural recordings of corticospinal volleys. Using this technique, Di Lazzaro and colleagues described a preferential activation of the I_1-wave by anteriorly oriented pulses at low threshold, whereas posteriorly oriented pulses tended to elicit later I-waves with a higher threshold. The order of I-wave recruitment and the relative latencies of the I-wave peaks were however not in all subjects exactly reversed with the opposite orientation, and the correlation between I-wave-amplitudes and MEP amplitude was not the same for either direction (Di Lazzaro et al., 2001), raising questions about the exact site of stimulation.

With regard to the motor threshold, it should be kept in mind that the stimulus intensity indicated by the hardware is only derived from the peak current in the initial ~50 μs of the pulse (Mr Kienle, Medtronic, personal communication). It does therefore not predict the physiological relevance of the latter parts of the damped oscillation, which may be different for the various waveforms even if the initial peak current is identical. Hence, it is important to indicate both intensity and waveform to precisely designate a given pulse.

In our study, the MEP input/output curves from monophasic posteriorly oriented pulse differed most strongly from the other types. It is tempting to speculate that the relatively strong stimuli required with that TMS condition (co)activate sets of interneurons that are different or more numerous than for the other types of TMS. Furthermore, the monophasic pulse is the most asymmetric one and there fore the fast initial current flow is least counterbalanced by the opposite current flow of the second quarter cycle.

Maccabee and colleagues hypothesized that the physiologically relevant part of the biphasic waveform is the second quarter cycle oriented oppositely to the initial quarter cycle (Maccabee et al., 1998). This was confirmed in vivo by Corthout and colleagues with regard to skotoma induction by stimulation over the visual cortex (Corthout et al., 2001).

Maccabee et al. (1998) also reported a biphasic waveform to be more effective than a monophasic one with regard to threshold of excitation and response amplitude. They offered two possible explanations. One was a role of the initial quarter cycle current inducing a hyperpolarization, thereby modifying the excitability of voltage-dependent sodium channels so as to be more excitable at the subsequent depolarisation. This is reminiscent of the anode-break stimulation explained by Roth (Roth, 1994). Another explanation was the longer duration of the depolarising second quarter cycle from the biphasic as compared to the monophasic pulse. Here we show differences between the half sine and the biphasic waveform, although the falling phase in the second quarter cycle of these waveforms is identical. This suggests that the difference between the monophasic and the biphasic waveforms might also involve the 3rd and 4th quarter cycle, and that these quarter cycles lower the motor threshold and reverse the influence of current direction with regard to motor threshold, MEP latency, and SP duration. A simple mechanism could be the longer duration of the biphasic as compared to the monophasic or the half sine pulse. Hence, our findings make a pivotal role of the initial hyperpolarization as suggested by Maccabee et al. (1998) less likely.

In an earlier paper, Brasil-Neto and colleagues studied the amplitudes and the latency of MEPs induced in a small hand muscle and systematically varied the orientation of figure-of-8 coils over the primary motor cortex (Brasil-Neto et al., 1992). They found an optimal MEP amplitude and the shortest latency with monophasic and biphasic pulses flowing anteriorly in the brain and approximately perpendicular to the presumed location of the central sulcus. Interestingly, for biphasic pulses at higher intensities, the orientational specificity was less marked, and another coil position yielding high amplitudes appeared about 180° opposite to the first. They concluded that the first and the second phase of the biphasic pulse become effective at higher intensities. Our data extend these results by showing that the current direction is of less pronounced relevance for the half sine and the biphasic pulse than for the monophasic pulse.

The results of the SP duration are consistent with a recent study where the authors compared monophasic pulses of anterior and posterior current direction with biphasic pulses with an initial anterior current direction (Orth and Rothwell, 2004). They used however a different set of stimulators, the Magstim 200 for monophasic pulses and the Magstim Super Rapid for biphasic pulses (The Magstim Company, Whitland, Dyfed, UK). Similar to our data, they found longer SP duration with monophasic posteriorly oriented pulses than with monophasic anteriorly oriented pulses, although that difference in their study was greater than in ours. The authors hypothesized that inhibitory interneurons might be best activated by posteriorly oriented currents. In that study, the biphasic pulse with an initial posterior direction yielded an SP duration that was close to, but not longer than the monophasic posteriorly oriented pulses. That slight difference might be due to variations of the pulse configurations obtained with other stimulators (see Fig. 1); in addition, in the earlier study, the stimulus intensity steps for SP determination were adjusted to the AMT, which results in different step width for AP and PA oriented monophasic pulses.

In summary, our data indicate that the stronger asymmetry of the monophasic pulse results in a more pronounced difference from biphasic pulses than the less asymmetric half sine pulse. In addition, the data suggest a relevance of the 3rd and 4th quarter cycle of the biphasic pulse with regard to the motor threshold, the MEP latency and the SP duration. The difference with regard to the MEP input/output curve further support the idea that mostly monophasic pulses activate a different subset of cortical interneurons.

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