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Transcranial magnetic stimulation modulation of corticospinal excitability by targeting cortical I-waves with biphasic paired-pulses

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Abstract

Background

Transcranial magnetic stimulation (TMS) induced I-wave behavior can be demonstrated at neuronal population level using paired-pulses and by observing short-interval cortical facilitation (SICF). Advancements in stimulator technology have made it possible to apply biphasic paired-pulses to induce SICF.

Objective

Our aim was to characterize the SICF I-wave interaction by biphasic paired-pulses with the ultimate objective to enhance TMS effects via SICF in various TMS-applications.

Methods

We used biphasic paired-pulses in 15 volunteers to characterize corticospinal SICF using various 1.2–8.0ms inter-stimulus intervals, and measuring SICF input-output response.

Results

SICF interaction with the first I-wave (I1) was observed in the output responses (motor evoked potentials; MEPs) in all subjects. Most subjects (≥80%) also exhibited later SICF I-wave interaction. SICF at I1 was present at all applied intensities below 140% of resting motor threshold. At I2, we observed SICF only with intensities just above motor threshold.

Conclusions

Biphasic paired pulses can reliably induce SICF shown by the facilitatory I-wave interaction, and could therefore be applied with repetitive bursts to enhance responsiveness to TMS.

Key words: Transcranial magnetic stimulation; Motor evoked potential; Short-interval intracortical facilitation; Indirect wave; Biomedical engineering; Motor cortex
**Introduction**

Indirect (I)-waves refer to oscillatory discharges of corticospinal fibers following transcranial magnetic stimulation (TMS) of the motor cortex [1-3]. I-waves can be visualized indirectly as an increase in motor responses (motor evoked potentials, MEPs) when applying paired-pulses with specific inter-stimulus intervals (ISIs) [1, 4, 5]. Typically, this short-interval intracortical facilitation (SICF) occurs and has been well documented when applying monophasic paired-pulses [4-7].

Recently we showed that biphasic paired-pulses can induce SICF [8].

Comparison between monophasic pulses and half-sine pulses has demonstrated that pulse-shape does affect SICF [6]. Examination on the differences in I-wave induction with biphasic and monophasic TMS has revealed that biphasic TMS produces a more complex pattern of cortical activation than the monophasic TMS [9], albeit all reported SICF results reflect complex neuronal population and network interactions. The I-wave characterization with TMS paired-pulses provides a unique opportunity to utilize brain’s own facilitatory mechanisms by synchronizing TMS with I-waves, hence potentially enhancing the responsiveness to TMS.

The aim of the present study was to characterize the SICF facilitatory I-wave interaction timing and effect strength with biphasic paired-pulse waveforms. Based on our previous findings [8], we hypothesize that clear SICF effects are to be observed and I-waves identified by output responses. Application of biphasic paired-pulse TMS may provide major advantages in enhancing TMS effects via SICF by maximizing the corticospinal motor output with paired-pulses.

**Materials and methods**

**Subjects**
We conducted the study in two experiments. Both experiments included 15 healthy, right-handed volunteers (experiment I: 6 females, age: 33±10 years; experiment II: 5 females, age: 32±11 years). Experiments were done on different days and on a different set of volunteers. The study was approved by the local ethical committee (permission 72/2016) and a written informed consent was obtained.

**Measurements**

Navigated TMS (nTMS) measurements were conducted with NBS System 4.3 prototype (Nexstim Plc., Helsinki, Finland) by using a figure-of-eight coil. For the nTMS, structural T1-weighted magnetic resonance images (MRIs) with a resolution of 1mm were acquired with a 3T MRI scanner (Philips Achieva 3.0T TX, Philips, The Netherlands). Electromyography (EMG) was measured from the relaxed first dorsal interosseous (FDI) muscle of the right hand during nTMS experiments using an integrated EMG device. Responses above 50µV were accepted as MEPs.

**Experiment I – characterizing the I-waves through SICF**

The optimal cortical motor representation, i.e., the location and coil direction inducing the highest amplitude MEPs for FDI, was mapped using single-pulse nTMS with the induced current direction on the cortex in AP-PA direction. At this location, the motor threshold (MT) was calculated by using single-pulses with the Motor Threshold Assessment Tool (MTAT) 2.0 [10, 11]. Thereafter, the stimulation was given at a stimulation intensity of the test pulse being 110% of MT and the second pulse being 90% of MT in paired-pulse sequences [8] using the ISIs: 1.2–5.0ms in 0.2ms intervals, and 5.3–8.0ms in 0.3ms intervals. In order to compare the effects induced by the paired-pulses, also two single-pulse sequences were applied with a stimulation intensity of 110% of MT, the first sequence near the beginning of the experiment and the second near the end placed semi-
randomly within the paired-pulse sequences. All sequences included 20 trials administered in random order at intervals of 4–6s. About one minute pause was held between the sequences.

Experiment II – input-output characteristics in SICF

The experiment started by roughly mapping the primary motor cortex to find the optimal cortical motor representation as in experiment I. At the optimal location, the MT was determined by using single-pulses with the NBS System 4.3 integrated MT calculation protocol, which we found to produce similar outcome with the MTAT used in Experiment I in our simulations (see Supplement 1). The input-output characteristics were determined with test pulse stimulation intensities of 90–140% of MT in 10% intervals for single-pulse and paired-pulses with the following ISIs: 1.4ms, 1.6ms, 2.8ms and 3.0ms to target I1- and I2-waves. In the paired-pulse sequences, the second pulse was always 82% of the test pulse intensity. Altogether 20 trials were given with each intensity in random order at 4–6s intervals. About one minute pause was held between the sequences.

Analysis of MEP peaks using a 5-peak Gaussian model

To analyze I-wave interaction through SICF induced by paired-pulse TMS, we applied a sum of five Gaussian curves adjusting the previous approach by Cirillo et al. [12] (Figure 1A). In our approach we applied fitting of five peaks to the experimental data estimating the occurrence of peaks via peak amplitude ($A$), peak latency ($t$), width ($\sigma$) for each peak $i$, and a common baseline ($y_0$) as follows:

\[ I_i(t) = A_i e^{\frac{(t-t_i)^2}{2\sigma_i}} \]  \hspace{1cm} (1)

\[ y(t) = y_0 + \sum_{i=1}^{5} I_i(t) \] \hspace{1cm} (2)

where $y$ is the normalized MEP amplitude at different ISIs ($t$). The parameters of the Gaussian model were fitted to experimental data constructed for each subject using bootstrapping for mean MEP amplitudes at different ISIs with 1000 repetitions. The fitting was performed using
multidimensional non-linear least-squares parameter optimization in Matlab (MathWorks, Inc., Natick, MA). Optimized parameter values for each subject were computed as the mean of the 1000 repetitions. Peaks with 95% confidence intervals (CIs) not going below normalized amplitude of 1 (single-pulse MEP amplitude) were considered significant, i.e. the occurrence of the peak was verified.

Data-analysis and statistics

MEPs with preceding muscle contraction were excluded from the analysis. In experiment I, from each paired-pulse sequence, the mean amplitude of the MEPs was normalized to the average MEP of the two single-pulse sequences. In experiment II the stimulation intensities were normalized to the MT of each subject. Thereafter, the mean MEP amplitude of each paired-pulse sequence was compared with that of single-pulse at specific stimulation intensity with paired-samples t-test. Levene’s test was applied to compare variances between optimal ISI between SICF interactions in different I-waves. Sidak adjustment was applied to correct p-values for multiple comparisons. The statistical analyses were performed in SPSS Statistics 22 (IBM Corporation, Somers, NY) and Matlab with the threshold for significance set to 0.05.

Results

All subjects demonstrated SICF. In the group average, I1-, I2-, and I3-wave interactions were present, as well as trends of I4- and I5-wave (Figure 1B). All subjects displayed SICF interaction with I1-waves (Figure 1C and 1D, Table S1). The occurrence rate decreased for later I-waves. The high occurrence rate demonstrates that SICF-interaction with later I-waves is present in $\geq 80\%$ of the subjects. There was significant differences between the variations of individual optimal ISIs ($t_i$) to produce SICF interaction with different I-waves. There were no significant differences between the variations of $t_1$ and $t_2$ ($p=0.073$). The $t_3$, $t_4$ and $t_5$ exhibited greater variation than $t_1$ ($p<0.013$), but
not with \( t_2 (p>0.06) \). In experiment 1, total of 727±9 pulses were given. The MTs were 40.5±10.2 
\%-MSO. The individual average single-pulse MEP amplitudes were 659±425µV.

In the input-output curves, we found significant differences in the MEP amplitudes induced by 
paired-pulse TMS at I1- and I2-waves when compared with single-pulse TMS. The MEP 
amplitudes from paired-pulse TMS were greater at lowest stimulation intensities indicating decrease 
of resting MT by SICF. The SICF effect diminished at higher applied intensities. At I1-wave, the 
MEP amplitudes were higher at all applied intensities, except 140%-MT, compared to single-pulse 
MEPs (Figure 2A). At I2-wave, the MEP amplitudes were not significantly different from those of 
the single-pulse TMS at the highest applied stimulation intensities of 130%-MT and 140%-MT, nor 
at the lowest intensity of 90%-MT (Figure 2B). Comparison of 1.4ms (I1) and 2.8ms (I2) MEP 
amplitudes at the different intensities revealed that the 1.4ms MEPs were higher in amplitude at 
intensities 90%-MT \((p=0.013)\) and 100%-MT \((p=0.021)\), while the differences were non-significant 
at higher intensities \((p≥0.603)\). In experiment 2, total of 613±17 pulses were given. The MTs were 
37.7±8.8 \%-MSO.

**Discussion**

We characterized the facilitatory I-wave interaction through SICF using MEPs to biphasic paired-pulse TMS. In all subjects, SICF interaction with I1-wave was observed. SICF at later I3, I4 and I5 
-waves displayed more individual characteristics than I1- and I2-waves, as the optimal ISI to induce 
SICF varied (Table S1). Input-output behavior with paired-pulses timed at I1- and I2-waves also 
displayed SICF. Even though inter-individual variation was observed in the SICF appearance, it 
was apparent that I1-wave induced SICF was the clearest.
Somewhat diffuse appearance of later I-waves provides indications of the inter-individual variation in motor cortical function. All subjects exhibited SICF at I1-waves, while the optimal ISI tended to vary more at ISIs past I2-waves (Figure 1C). Earlier, Cash et al. reported with monophasic paired-pulses that 5/22 subjects did not present SICF or long-interval cortical facilitation with any ISI tested [13]. Recent simulation study showed that the excitation-inhibition balance, as well as the structure of the cortical layers affect appearance of later I-waves [14]. Greater excitation-inhibition ratio induces a greater number (and greater temporal variation) of I-waves, explaining the appearance of later I-waves, while conductance increase in GABA cause later I-wave amplitudes to decrease [14]. Overall, it appears that elevated excitability causes an increase in later I-waves, however, with larger temporal variation. The SICF disappears after I1 when muscle is activated during TMS [4].

We found that using biphasic paired-pulses to induce I-waves, multiple, at least five, I-waves can be demonstrated (Figure 1C). However, the I5-wave does not display as clear SICF effect in the group average data as the earlier waves (Figure 1B), even though it was identified in most subjects. In epidural measurements, five I-waves have been reported with higher TMS intensities than those used in the present study [9].

The observations on non-significant SICF in the I1-wave and I2-wave targeted paired-pulse responses in the IO-curves at highest applied intensities (Figure 2) could be explained by the technical limitation of our stimulator due to which the intensity of the second pulse was linked to the intensity of the first pulse. Setting the stimulation intensity of the second pulse to 82% to that of the first stimulus leads to the second stimulus becoming suprathreshold for the highest two intensities (130%-MT and 140%-MT), which may interfere with the I-wave interaction [15].

There are characteristic differences in evocation of I-waves between biphasic and monophasic pulses [2, 9, 16]. Present data suggests that due to less specific directionality of the biphasic
stimulation [17], the different I-waves could be more easily, but less specifically, induced. While the overall mechanisms of the different I-waves possess variation between subjects, the complexity and subject-specificity of induction from the early I-waves towards later I-waves increases, as was observed in the occurrence rates of SICF (Figure 1D). Instead, the group average I-wave curve (Figure 1B) shows overall dampening of the SICF at longer ISIs explained by the finding that the optimal ISIs to induce the later I-waves become more subject-specific (Figure 1A). A rough comparison between the data of the present study (biphasic paired-pulses) and that from the earlier study by Ziemann et al. [4] (monophasic paired-pulses), implies that biphasic paired-pulses could give arise stronger SICF (Figure 1B). However, the comparison is only suggestive, as the study protocols differed between these studies.

Cash et al. studied the combination of SICF and late cortical disinhibition in augmenting plasticity [13], and demonstrated that even short stimulus sequences (less than 1 minute) can produce long-lasting (up to 60 min) plasticity. This highlights the potential if SICF I-wave interaction in therapeutic applications, which could potentially be enhanced using biphasic paired-pulse TMS. The potential application can also be extended to diagnostic use of TMS. In therapy stimulations, I-wave targeted stimulation could be applied in bursts mixed with conventional rTMS to potentially enhance the rTMS effect. In addition, diagnostic utilization of single-pulse TMS could benefit from SICF induced biphasic paired-pulses, as lower stimulation intensities are required [8]. Intuitively thinking, lower stimulation intensity means more focality in stimulation, i.e. cortical mapping procedures could become more reliable, as well as very local modulation of intrinsic oscillatory behaviors in human brain. Due to generally lowered threshold for MEP induction due to SICF, more challenging subjects could be studied, or cortical neural structure impairments detected. The true potential of these and other applications need to be examined and verified in future studies. To
optimize effectiveness of such protocols individually optimized ISIs for maximum SICF should be used [18].

Conclusions

We found that facilitatory I-wave interaction can be induced using biphasic paired-pulses, and the overall excitability of motor system modulated most efficiently when the paired-pulse TMS is timed to the first I-wave. Due to effective induction, the potential of SICF-based therapy protocols should be studied, and enhancement of overall single-trial TMS effects further utilized for potentially wider range of diagnostic and therapeutic applications.

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Conflicts of interest: GJ, PS and JK are employed by Nexstim Plc, Helsinki, Finland. PJ has received unrelated consulting pay from Nexstim Plc. EK has received unrelated travel support from Nexstim Plc.

References


Figure 1: A) A 5-peak Gaussian model was fitted to estimate the interaction of SICF with I-waves in each subject. The vertical dotted lines indicate the latency ($t$) of each peak and the horizontal dashed line represents the size of the single-pulse MEP. Amplitude and width parameters fitted using the model are indicated for the first peak. B) SICF interaction with I-waves demonstrated using biphasic paired-pulses. The paired-pulse MEP amplitudes were normalized to the single-pulse MEPs. Error bars indicate positive standard error of mean. Black dots indicate significant SICF effect ($p < 0.05$, Sidak corrected), grey dots indicate significant SICF effect ($p < 0.05$, uncorrected) and white dots non-significant effect. For comparison, I-waves demonstrated through SICF induced by monophasic paired-pulse TMS are shown traced from the study by Ziemann et al. [4].
individual fitted 5-peak Gaussian model is presented with thick grey line. C) Mean peak amplitudes $(A_i + y_0)$, at different ISIs ($t_i$) shown with the standard deviations. The size of grey markers is indicative of the width of the peaks ($\sigma_i$). It is observed that the individually optimized ISIs for different peaks vary more from first peak towards the last peak. D) The occurrence of SICF is indicating that interaction with five I-waves were identified in 12/15 of the subjects.
Figure 2: Input-output curves for single-pulse MEPs and paired-pulse MEPs targeted at different I-waves. SICF effect is clear in paired-pulse TMS timed at the I1 (A) and I2 –wave (B). Dashed lines indicated standard error mean. * indicates significant difference between single-pulse and paired-pulse responses (Sidak corrected $p < 0.05$).
A) MEP amplitude (\(-\)) normalized to single-pulse

Inter-stimulus interval (ms)

First peak
Second peak
Third peak
Fourth peak
Fifth peak

B) Present study
Ziemann et al., 1998

Biphasic
Monophasic

Group mean of fitted 5-peak Gaussian models

C) Peak amplitude (\(-\)) normalized to single-pulse MEP

Inter-stimulus interval (ms)

D) Occurrence rate of SICF (%)

Interacting I-wave