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Technical note

Facilitatory effect of paired-pulse stimulation by transcranial magnetic stimulation with biphasic wave-form

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ABSTRACT

Transcranial magnetic stimulation (TMS) is used to probe corticospinal excitability by stimulating the motor cortex. Our aim was to enhance the effects of biphasic TMS by coupling a suprathreshold test pulse and a following subthreshold priming pulse to induce short-interval intracortical facilitation (SICF), which is conventionally produced with monophasic TMS. Biphasic TMS could potentially induce the SICF effect with better energy-efficiency and with lower stimulus intensities. This would make the biphasic paired-pulses better applicable in patients with reduced cortical excitability.

A prototype stimulator was built to produce biphasic paired-pulses. Resting motor thresholds (rMTs) from the right and left hand abductor pollicis brevis muscles, and the right tibialis anterior muscle of eight healthy volunteers were determined using single-pulse paradigm with neuronavigated TMS. The rMTs and MEPs were measured using single-pulses and three paired-pulse setups (interstimulus interval, ISI of 3, 7 or 15 ms).

The rMTs were lower and MEPs were higher with biphasic paired-pulses compared to single-pulses. The SICF effect was greatest at 3 ms ISI. This suggests that the application of biphasic paired-pulses to enhance stimulation effects is possible.

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1. Introduction

Transcranial magnetic stimulation (TMS) enables non-invasive assessment of corticospinal excitability (CSE) by stimulating the human brain. Most often, CSE is measured through motor responses after targeting TMS to the primary motor cortex [1,2]. A common measure for CSE is the motor threshold (MT), which is often determined by finding the lowest possible stimulation intensity that produces measurable motor evoked potentials (MEPs) in the target muscles on the contralateral side [3,4]. CSE can be modulated using paired-pulses of TMS. Different paired-pulse protocols can be used either to facilitate or inhibit responses by modulating CSE at the stimulated area and the connected corticospinal tract [5–8]. The effect of the paired-pulses is dependent on the interstimulus interval (ISI), and the stimulation intensities applied [5–7].

Conventionally in the paired-pulse TMS two consecutive magnetic stimuli are given, the first one, conditioning stimulus, at a subthreshold intensity and the following test stimulus at a suprathreshold intensity [5,9,10]. A wide range of ISIs can be applied to achieve inhibitory and facilitatory effects. Low ISIs of 1–5 ms induce short-interval cortical inhibition (SICI), while longer ISIs of 7–20 ms induce intracortical facilitation (ICF) [5]. Longer ISIs have also been used to achieve inhibitory and facilitatory effects [11,12]. If the test pulse is given first, then a subthreshold priming pulse given within a short ISI window can induce modulation effects, namely short-interval intracortical facilitation (SICF) [6,8,13]. SICF has been demonstrated to have a facilitatory I-wave interaction by paired-pulse TMS [8]. SICF can be achieved with ISIs of about ~1.5 ms, ~3.0 ms and ~4.5 ms [6,8,13].

Studies on paired-pulse TMS are conducted using monophasic stimulation pulse wave-form because of the high recovery rate of the stimulation pulses. Compared to the other common pulse wave-form of biphasic type, monophasic pulses are less energy-efficient and require more power to produce a similar effect in the cortex often demonstrated by systematic differences in MTs

Abbreviations: APB, Abductor pollicis brevis; CSE, Corticospinal excitability; EMG, Electromyography; GABA, Gamma-aminobutyric acid; ICF, Intracortical facilitation; ISI, Interstimulus interval; MEP, Motor evoked potential; MT, Motor threshold; rMT, Resting motor threshold; SICF, Short-interval intracortical facilitation; SICI, Short-interval intracortical inhibition; TA, Tibialis anterior; TMS, Transcranial magnetic stimulation.

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[14-16]. Hence, paired-pulse TMS in patients with lowered level of CSE cannot be performed as often. For instance, stroke patients and medicated epilepsy patients often exhibit significantly decreased CSE [17-20], and therefore the use of monophasic pulses with those patients limits the applicability of TMS. Certain drugs, especially voltage-gated ion channel blockers have been shown to decrease CSE limiting the applicability of TMS [21]. Biphasic pulses have not been used with short ISIs to produce paired-pulses due to their relatively low pulse recovery rate considering the ISIs required producing wanted effects.

The aim of this study was to utilize a prototype TMS device able to produce biphasic paired-pulses to modulate CSE potentially through SICF. This effort was made to enable paired-pulse protocols with better energy-efficiency compared to monophasic pulses in patients with lowered CSE and to enhance the effects of TMS by priming the test pulse with the following subthreshold pulse.

2. Materials and methods

2.1. Subjects

Eight healthy right-handed volunteers participated in this study (age 42 ± 8 years, 7 males). The study was performed at the research laboratory of Nexstim Plc with ethical permission from the Hospital District of Northern Savo research ethics committee (41/2014). All subjects gave a written informed consent prior to the experiments.

2.2. Instrumentation

We used a custom-made stimulator, a prototype based on a Nexstim NBS stimulator, which was able to produce biphasic stimulation at pre-specified ISIs. The navigated TMS system consisted otherwise from a pre-clinical NBS version 4.2 (Nexstim Plc, Helsinki, Finland). An integrated electromyography (EMG) device was used to record and monitor muscle responses from the left and right abductor pollicis (APB) muscles and right tibialis anterior (TA) muscle (1450 Hz sampling rate) using disposable Ag–AgCl surface electrodes.

A three-dimensional brain surface was reconstructed based on the MR images to a depth of 20–25 mm from the scalp to visualize the mapping surface at the region of the anatomical hand knob [14]. At this depth, anatomical structures were easily identified.

2.3. Stimulation protocol

The stimulation procedure was begun by locating the primary motor cortex by stimulating the cortex using neuronavigated TMS at suprathreshold intensity and finding the hotspot for the target muscles from the contralateral side [22]. Coil rotation angle was optimized at the hotspots to find the final target setup for the stimulation [22,23]. At the muscle-specific targets, resting motor thresholds (rMTs) were determined from the subjects using single-pulse adaptive paradigm with MEP threshold amplitude of 50 μV [3,24]. Then, 20 single-pulse MEPs were gathered at an intensity of 110% of single-pulse rMT. Subsequently, rMTs and MEPs were measured using 3 paired-pulse setups (ISI = 3 ms, 7 ms or 15 ms) from all muscles (Fig. 1). For technical convenience, rMTs for the paired-pulses were determined using Rossini–Rothwell method [4,25] justified by reported indifference in rMT values between the two methods [26]. In the paired-pulses, the stimulus intensity of the second, priming pulse was 82% of the first, test pulse intensity. 20 paired-pulse MEPs were recorded at each ISI from each investigated muscle with test pulse intensity of 110% of single-pulse rMT. The priming pulse intensity was 82% of the test pulse intensity, i.e. ∼90% of the single-pulse rMT.

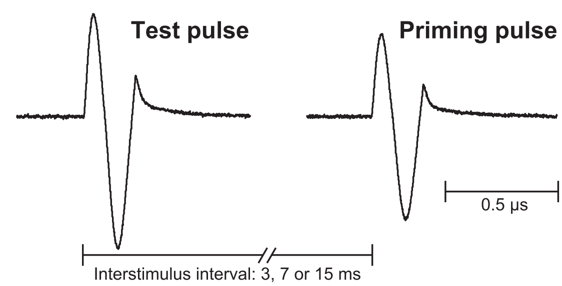

Fig. 1. Pulse characteristics.
Measured biphasic pulse shapes for test and priming pulses using a measurement coil and oscilloscope. The ISI between the test and priming pulse onsets was 3, 7, or 15 ms. The time-scale for the pulse images is given on the right.

2.4. Analysis

The EMG was analyzed using customized NBS software. Amplitudes of MEPs were measured peak-to-peak for each response in the EMG of all three muscles. Any responses contaminated with muscle activity within 100 ms pre-stimulus time were ignored in the analysis. MEPs with amplitude lower than 50 μV were considered as non-responses.

Repeated measures ANOVA was used to assess effects between the different ISIs and hemispheres. The APB and TA muscle analyses were separated from each other, since inter-hemispheric effect could only be investigated in the APB muscles. Mauchly's Test of Sphericity was used to test sphericity of the data, and Greenhouse-Geisser adjustment was conducted when necessary. Post-hoc comparisons were performed with respect to single-pulse TMS by bootstrapping 10,000 mean values in a pair-wise manner. The statistical analyses were performed with SPSS Statistics 22 (IBM Corporation, Somers, NY) and Matlab 8.4 (MathWorks Inc, Natick, MA) with threshold for statistical significance set to $p<0.05$.

3. Results

We were able to locate the target stimulation areas to all muscles in all subjects. Data from one subject's right TA muscle had to be rejected due to technical difficulties in data storing. We found that ISI had a clear facilitatory effect on the rMTs and MEPs with biphasic paired-pulses (Figs. 2 and 3) indicating modulation of the CSE through biphasic paired-pulses. Repeated measures ANOVA showed that ISI had a significant effect on the rMT in the APB muscle ($F=11.65$, $p<0.001$, Fig. 2) and the TA muscle ($F=3.63$, $p=0.033$). Correspondingly, ISI had a significant effect on the MEP amplitude in the APB muscle ($F=4.65$, $p=0.048$, Fig. 2) and the TA muscle ($F=4.81$, $p=0.015$). There were no differences between the hemispheres in either rMTs or MEPs. No ISI x hemisphere interaction was observed. The rMTs were significantly decreased in all the muscles at 3 ms ISI as well as with 7 ms ISI in right APB and TA muscle. The average decrease in rMTs at ISI of 3 ms were 12% in the right APB, 7% in the left APB and 11% in the right TA. The average decrease in rMTs at ISI of 7 ms was 6% in the right APB and 8% in the right TA. More profoundly, the resting MEPs were affected by the paired-pulses as well with all muscles demonstrating significant SICF effect with all ISIs in right TA. The average in the MEP amplitudes at ISI of 3 ms were 270% in the right APB, 207% in the left APB and 222% in the right TA, 219% in the right TA at ISI of 7 ms and 360% in the right TA at ISI of 15 ms.

4. Discussion

In the present study, we found that paired-pulse TMS conducted using biphasic pulses was able to decrease rMT and

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