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# Enhancement of Neuromodulation with Novel Pulse Shapes Generated by Controllable Pulse Parameter Transcranial Magnetic Stimulation

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ABSTRACT

*Background:* Standard repetitive transcranial magnetic stimulation (rTMS) devices generate bidirectional biphasic sinusoidal pulses that are energy efficient, but may be less effective than monophasic pulses that induce a more unidirectional electric field. To enable pulse shape optimization, we developed a controllable pulse parameter TMS (cTMS) device.
*Objective:* We quantified changes in cortical excitability produced by conventional sinusoidal bidirectional pulses and by three rectangular-shaped cTMS pulses, one bidirectional and two unidirectional (in opposite directions), and compared their efficacy in modulating motor evoked potentials (MEPs) produced by stimulation of motor cortex.
*Methods:* Thirteen healthy subjects completed four sessions of 1 Hz rTMS of the left motor cortex. In each session, the rTMS electric field pulse had one of the four shapes. Excitability changes due to rTMS were measured by applying probe TMS pulses before and after rTMS, and comparing resultant MEP amplitudes. Separately, we measured the latency of the MEPs evoked by each of the four pulses.
*Results:* While the three cTMS pulses generated significant mean inhibitory effects in the subject group, the conventional biphasic cosine pulses did not. The strongest inhibition resulted from a rectangular unidirectional pulse with dominant induced current in the posterior–anterior direction. The MEP latency depended significantly on the pulse shape.
*Conclusions:* The pulse shape is an important factor in rTMS-induced neuromodulation. The standard cosine biphasic pulse showed the smallest effect on cortical excitability, while the greatest inhibition was observed for an asymmetric, unidirectional, rectangular pulse. Differences in MEP latency across the various rTMS pulse shapes suggest activation of distinct subsets of cortical microcircuitry.

## Introduction

Transcranial magnetic stimulation (TMS) is an established technique for noninvasive brain stimulation. In addition to evoking action potentials in neurons with single strong magnetic pulses, repetitive TMS (rTMS) protocols modulate the endogenous activity of brain circuits by either increasing or reducing excitability [1–3]. Neuromodulation with rTMS is an indispensable technique in experimental brain sciences [4–6] and a promising tool in neurology and psychiatry that is FDA-approved for the treatment of depression [7–15].

Although rTMS serves well as a noninvasive tool for studying basic scientific questions in sufficiently large subject groups, the strength of neuromodulatory effects is relatively low and competes with often stronger ongoing endogenous activity in the brain, resulting in substantial variability of the neuromodulatory effects within and across subjects [16–20]. This is unfortunate for both neuroscientific and therapeutic applications, where strong and reliable effects are desired.

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However, neuromodulatory effects in in-vivo and in-vitro animal studies suggest that stronger effects may be possible [21–24].

Various parameters of rTMS have been studied to increase efficacy [25–29], including pulse repetition rate [21,30–32] and coil size and shape [33]. In comparison, the influence of the pulse shape, i.e., the coil current or the induced electric field waveform as a function of time, has been considered only within narrow limits [34–41]. This has been due primarily to technological reasons, as currently available devices can only generate a few distinct pulse shapes [42]. At present, rTMS neuromodulation is almost exclusively induced with sinusoidal biphasic pulses, although experiments in the primary motor cortex have shown that this pulse shape has a relatively low neuromodulation strength relative to other shapes, such as sinusoidal monophasic [2,34,38–41]. Unfortunately, pulse shapes that are more effective cannot be generated at train frequencies greater than approximately 1–2 Hz with standard devices [43,44]. Furthermore, the parameter space of pulse shapes has barely been explored, again primarily due to technological limitations, and it is unknown which characteristics render a pulse more effective or how pulses could be optimized.

To address these technological limitations we developed a controllable pulse parameter TMS (cTMS) device that enables the efficient generation of pulses with various shapes [45,46]. In the present study, we used a cTMS device and a standard rTMS device to stimulate motor cortex to compare the average effects on motor evoked potential (MEP) amplitude of 1 Hz trains of several novel types of pulse shapes with the standard biphasic sinusoidal pulse. rTMS with 1 Hz trains tends to have an inhibitory effect, and is therefore a relatively safe paradigm to explore novel pulse shapes with unknown effects. We programmed the cTMS device to produce a rectangular bidirectional pulse shape, as well as a rectangular predominantly unidirectional pulse shape with amplitudes of the anterior–posterior (AP) and posterior–anterior (PA) electric field phases that differed by more than fivefold. These pulses were designed such that they can be generated efficiently using cTMS at high repetition rates in subsequent excitatory mono-frequency and theta-burst protocols [47–49].

In addition, there are various options for probing the cortical excitability change in MEPs from pre to post rTMS intervention, and there is currently no consensus on the best approach. While several studies compared different rTMS pulse shapes by probing MEP excitability with the pulse type used for the rTMS intervention [35,38,39], others use the same monophasic shape for the test probe regardless of the rTMS condition [40,50–52]. However, the apparent excitability change resulting from rTMS can vary when detected with different probing pulse types [18,34]. Specifically, in inhibitory protocols, monophasic probing pulses result in larger apparent changes in MEP amplitude than biphasic probing pulses. To our knowledge, the effects of the directionality of the probing pulses have not yet been studied, and therefore we quantified the influence of different probing pulse conditions (directionality and amplitude) in pre- and post-intervention testing.

## Materials and methods

### Subjects

Twenty-one healthy subjects (median age 21, age range 18–48 years, 14 female, 7 male, all right-handed) were recruited and provided written informed consent. The study was approved by the Duke University Medical School IRB. Subjects were excluded if they had a history of any Axis I DSM-IV psychiatric disorder including substance abuse or dependence, as well as any current medications or history of any neurological disease or other illness that would present a risk with TMS or would potentially confound effects of TMS on cortical excitability. All subjects were screened with urine drug tests to verify reported use. Women of childbearing capacity underwent a pregnancy test. Subjects were tested for right-handedness (modified Edinburgh handedness questionnaire). Thirteen subjects completed all rTMS sessions of the study (8 female, 5 male, age range 18–44). The other eight subjects dropped out or were excluded due to very high stimulation thresholds that precluded implementation of the experimental procedure (3 subjects), repeated no-shows, or withdrawal for personal reasons. Participants were questioned concerning side effects of TMS in each TMS session.

### Study design

The study comprised five sessions. In the first session, we applied single TMS pulses spaced at least 7 s apart to the left primary motor cortex to familiarize the subject with the setup, test tolerability, determine motor thresholds, measure motor evoked potential (MEP) latencies, and calibrate the robotic coil holder for the study (see below). In the remaining four sessions, we tested four different rTMS pulse conditions in the primary motor cortex. Each of these sessions was performed exclusively with a different rTMS pulse shape so that every subject received all four conditions. The sequence of the conditions within a subject was counterbalanced across subjects. The effectiveness of counterbalancing was ascertained with a nominal logistic model with session number as independent variable and rTMS type as dependent variable as well as a Pearson Chi$^2$ test, none of which were significant ($p > 0.577$ and $p > 0.630$, respectively). The rTMS sessions were at least five days apart, and started approximately at the same time of day for each subject (±1 h).

### Repetitive TMS

In each rTMS session, after estimation of the motor threshold and coil positioning, subjects received 80 test pulses, taking about 13 minutes, followed by a 1000 s (16 min, 40 s) rTMS train. This was immediately followed by a series of 180 test pulses, which took approximately 30 minutes (see Fig. 1).

The rTMS interventions consisted of 1000 pulses of one of the four rTMS pulse types at a pulse rate of 1 Hz with a stimulation strength of 97.5% of the individual resting motor threshold, defined as the pulse amplitude producing an average peak-to-peak MEP amplitude of 50 μV. This choice of pulse amplitude was based on the following considerations. Prior studies of similar design showing stronger inhibitory effect of monophasic versus biphasic sinusoidal pulses were conducted at subthreshold intensity (90% of resting motor threshold) [34,35]. On the other hand, for biphasic pulses, as in this study, inhibitory effects have been reported for stimulation strengths between 90% and 125% of motor threshold [1,3,19,33,35,52–56], with evidence that stronger rTMS stimuli are more effective [33,52,57]. Therefore, we chose to use a stimulus intensity that is higher than 90% of motor threshold, potentially increasing the likelihood of significant inhibitory effects, but that is not too high so as not to saturate possible pulse-shape-dependent selective neural recruitment effects in the cortex and to limit spinal modulation effects [19,58]. Of course, the motor threshold is not an abrupt cutoff for motor responses but is rather a point on the continuous recruitment curve that corresponds to a specific but arbitrary average MEP amplitude (50 μV here, as standard in TMS). Thus, our choice of stimulus intensity is one of many possible levels on the motor recruitment curve that is within the range for reported inhibitory effects.

The four different rTMS pulses (see Fig. 2) comprise: