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Short communication

Method to assess the mismatch between the measured and nominal parameters of transcranial magnetic stimulation devices

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ABSTRACT

Background: Small variations in TMS parameters, such as pulse frequency and amplitude may elicit distinct neurophysiological responses. Assessing the mismatch between nominal and experimental parameters of TMS stimulators is essential for safe application and comparisons of results across studies.

New method: A search coil was used to assess exactness and precision errors of amplitude and timing parameters such as interstimulus interval, the period of pulse repetition, and intertrain interval of TMS devices. The method was validated using simulated pulses and applied to six commercial stimulators in single-pulse (spTMS), paired-pulse (ppTMS), and repetitive (rTMS) protocols, working at several combinations of intensities and frequencies.

Results: In a simulated signal, the maximum exactness error was 1.7% for spTMS and the maximum precision error 1.9% for ppTMS. Three out of six TMS commercial devices showed exactness and precision errors in spTMS amplitude higher than 5%. Moreover, two devices showed amplitude exactness errors higher than 5% in rTMS with parameters suggested by the manufactures.

Comparison with existing methods: Currently available tools allow characterization of induced electric field intensity and focality, and pulse waveforms of a single TMS pulse. Our method assesses the mismatch between nominal and experimental values in spTMS, ppTMS and rTMS protocols through the exactness and precision errors of amplitude and timing parameters.

Conclusion: This study highlights the importance of evaluating the physical characteristics of TMS devices and protocols, and provides a method for on-site quality assessment of multiple stimulation protocols in clinical and research environments.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive technique for brain stimulation that consists of an intense, brief magnetic pulse applied over the scalp, which induces an electric field capable of depolarizing neurons in the cerebral cortex. TMS is a powerful tool to assess cortical excitability and to treat many neurological disorders, such as depression and schizophrenia (Rossini et al., 2015). However, reproducibility of TMS physiological responses can be challenging mostly due to interindividual differences in anatomy (Opitz et al., 2013), brain states (Ferreri et al., 2014) and stimulation parameters (Hannah and Rothwell, 2017; Rothkegel et al., 2010; Souza et al., 2017). Moreover, it is well known that small variations in TMS parameters such as pulse amplitude, stimulation frequency, inter-train

Abbreviations: EMF, electromotive force; ITI, inter-train interval; ISI, paired inter-stimulus interval; ppTMS, paired-pulse transcranial magnetic stimulation; PPR, period of pulse repetition; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; spTMS, single pulse transcranial magnetic stimulation; TMS, transcranial magnetic stimulation

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interval (ITI), and waveform shape might induce distinct physiological outcomes (Arns et al., 2010; Cash et al., 2017; Koponen et al., 2018; Peterchev et al., 2014)

Several strategies are adopted to decrease variability in TMS responses, for instance, coil placement using neuronavigation systems (Ruohonen and Karhu, 2010; Souza et al., 2018a), and adjustment of stimulus intensity according to individual motor or phosphene thresholds (Deblieck et al., 2008). However, these strategies do not consider possible changes arising from limitations of the electronic components, the materials wear or equipment fatigue.

Recently, Nieminen et al. (2015) proposed a method to characterize the induced electric field of single-pulse TMS (spTMS) and compared the results among different coil geometries and stimulation devices. Even though such method has opened opportunities to evaluate the physical characteristics of the spTMS, it is not sufficient to infer about the quality of TMS devices during different stimulation protocols.

This study aimed to develop and validate a method to assess the mismatch between experimental and nominal TMS parameters in commonly used stimulation protocols to ensure safe applications. The analysis was performed in spTMS, paired-pulse (ppTMS), and repetitive (rTMS) protocols based on systematic (exactness) and random (precision) errors (JCGM, 2012; Prenesti and Gosmaro, 2015) of measured amplitude, interstimulus interval (ISI), the period of pulse repetition (PPR), and ITI. The technique was validated using simulated data and applied to six commercial stimulators working at several combinations of intensities and frequencies relevant for clinical and research applications (Lefaucheur et al., 2014).

2. Material and methods

2.1. Method for acquisition of induced EMF

To assess the mismatch of nominal and experimental values in stimulation protocols of commercial TMS devices, we measured the EMF induced by the magnetic flux of the TMS over a search coil. The search coil was made with copper wire of 0.25 mm diameter (AWG 30), with two turns and radius of 2 mm (Thielscher and Kammer, 2004). The search coil was attached to a three-axis acrylic step positioner with 1 mm resolution and placed concentrically to one of the TMS coil windings, ensuring the same coordinates relative to the coils in different acquisition runs. Besides, the search coil concentric to the TMS coil winding maximizes the magnetic field flux and its homogeneity (Fig. 1 - SM).

The EMF was digitized with the oscilloscope board NI PXI-5124 (National Instruments, USA) at a sampling frequency of 1 MHz, 12-bit resolution and anti-aliasing filter. The NI PXI-5124 is a high-performance oscilloscope, with sampling rate up to 200 MS/s. However, any analog-to-digital converter with sampling rate superior to 1 MHz can be used.

2.2. TMS protocols

To evaluate whether TMS devices were working as proposed by the manufacturers, we analyzed the three most commonly used protocols (spTMS, rTMS, and ppTMS) with the following stimulation parameters:

spTMS: ten pulses were acquired for each nominal amplitude from 20% to 100% in steps of 10%.

ppTMS: ten pulse pairs were acquired with ISI of 2 ms for each amplitude from 20% to 100% in steps of 10%.

rTMS: the PPR was adjusted as 0.5, 1, 5, 10, 15, 20, 25 and 30 Hz for all devices, extending for 40, 50, 60, 70, 80, 90 and 100 Hz for Magpro X100. For each combination of amplitude and frequency, ten pulses were recorded with nominal amplitude varying from 20% to 100% in steps of 10%. For ITI evaluation, ten pulses were recorded at intervals of 1 s and 5 s, with the nominal intensity at 50% and rTMS frequency at 10 Hz.

The rTMS and ppTMS stimulation protocols are detailed in the Supplementary Materials Table 1 – SM. Nominal values were based on standard clinical trials described elsewhere (Rossini et al., 2015).

2.3. EMF feature extraction

The methods used to extract the pulse parameters were developed and implemented in the EMF Analysis module of the SignalHunter software program (Souza et al., 2018b). The SignalHunter is a collaborative open source, GUI-based toolbox for electrophysiological data analysis written in Matlab 2015a (Mathworks, USA).

First, we defined a baseline with the signal recorded from 0.6 to 0.1 ms immediately before the magnetic pulse for the EMF recorded in every tested protocol. Mean and standard deviation (SD) were computed from the signal baseline. Then, pulse start was selected as the last data point after the baseline and before EMF achieves a value higher than the mean ± 2*SD. Pulse end was selected as the first value at least 200 μs after the pulse peak and inside the interval defined by the baseline mean ± 2*SD.

From each EMF signal recorded from the spTMS protocols, we extracted the pulse duration (total time of the EMF pulse), pulse rise time (time from pulse start to pulse peak), and amplitude (from zero-to-peak), illustrated in Fig. 2 – SM. Additionally, for ppTMS protocols, we extracted the pulse amplitude and ISI, defined as the time interval from the start of the first pulse to the start of the second pulse. Note that the definition of ISI used in our study follows the same definitions as Lefaucheur et al. (2014) and Rossini et al. (2015), and may differ from some definitions in psychology, which consider the ISI as the time between first stimulus offset and second stimulus onset (Yaremko et al., 2013). For rTMS protocols, we extracted the pulse amplitude, rTMS frequency (inverse of the PPR representing the time interval between two consecutive pulses into an rTMS train) and ITI (time interval from the end of the last pulse from the first train to the start of the first pulse from the second train). The maximum magnetic field intensity was calculated by numerical integration of the EMF (Nieminen et al., 2015).

2.4. Mismatch analysis method

Our mismatch analysis was based on measurements of exactness and precision errors, following the definitions by Prenesti and Gosmaro, (2015). Exactness quantifies the difference between the average of experimental measurements and a reference value representing the systematic errors, defined by Eq. 1. In turn, precision quantifies the standard deviation of the experimental measurements to represent the random errors associated with the measurements, represented by Eq. 2.

$$E = \frac{\sum (X_{exp})}{N} - X_{nom} \quad (1)$$

$$P = \sqrt{\frac{1}{N}\sum (X_{exp} - \bar{X})^2} \quad (2)$$

where E is the exactness error, N is the number of samples, X_{exp} is the experimental value, X_{nom} is the nominal value set in the stimulator, $\bar{X}$ is the average value and P is the precision error in percentage.

The mismatch analysis was applied to estimate the exactness and precision errors of measured pulse amplitude, PPR, ISI, and ITI for protocols of spTMS, ppTMS, and rTMS. The amplitude values of EMF were normalized (in percentage) by the average amplitude of 10 spTMS pulses at 100% of device output. The experimental values of PPR, ISI, and ITI were normalized by their respective nominal values. The evaluated parameters presenting exactness or precision errors greater than ± 5% were considered unsuitable for TMS reproducibility. The selected ± 5% error reflects variations that can potentially induce altered biological response for each stimulation parameters, such as amplitude (Pearce et al., 2013), rTMS frequency (Arns et al., 2010), and ppTMS ISI (Du et al., 2014).

To validate and evaluate the proposed method, we applied the mismatch analysis for simulated data from a signal generator and then, for the EMF recorded from six different commercial TMS devices operating at spTMS, rTMS, and ppTMS protocols in both experiments. In addition to the mismatch analysis, we performed the waveform characterization of magnetic pulses from commercial TMS devices, calculating the mean and SD of the rise time, pulse duration, and maximum magnetic field intensity, illustrated in Fig. 2 – SM.

2.5. Validation with simulated data

Sine pulses of 100 μs and 300 μs total duration and amplitude of 0.5 V were generated with a 33521A Function Generator (Agilent, USA). The simulated pulses provided the parameters necessary to validate the mismatch analysis method. The amplitude, frequency, and pulse width resolution were 0.001 V, 1 μHz and 1 ps, respectively. We also performed the waveform characterization of the simulated pulses, calculating the mean and SD of the rise time, pulse duration, and pulse amplitude. The nominal rise time was defined as the elapsed time for the sine wave to reach the maximum amplitude, equivalent to one-quarter of total pulse duration (25 μs and 75 μs for the 100 μs and 300 μs pulse durations, respectively).

Simulated pulses were digitized using the oscilloscope board NI PXI-5124 with a sampling frequency of 1 MHz, 12-bit resolution and anti-aliasing filter (National Instruments, USA) connected to the function generator by a BNC cable.

TMS protocols were simulated by selecting different ISI values between pulses. The spTMS protocol was simulated with 2 s of ISI, and ppTMS with 1 and 2 ms of ISI. In turn, rTMS protocols were simulated with ISI decreasing from 1 s (1 Hz) to 10 ms (100 Hz), representing the 1, 10, 20, 40, 50, 80 and 100 Hz of rTMS frequencies. Ten pulses were acquired for each protocol.

2.6. Mismatch analysis in commercial TMS devices

Mismatch analysis was performed in pulse parameters and TMS protocols described in Section 2.2. Six commercially available TMS stimulators connected to their correspondent figure-of-eight coils were evaluated: MagPro X100 with MagOption charging module and Cool-B70 coil; MagPro Compact with C-B60 coil (MagVenture Inc., USA); BiStim^2 with D70 mm Remote Control Coil (The Magstim Company Limited, UK); Neuro-MS/D with AFEC-02-100-C coil; Neuro-MS with the FEC-02-100 coil (Neurosoft, Russia) and Neuro-MS/A (Analogical) with the FEC-02-100 coil (Neurosoft, Russia). Biphasic magnetic pulses were selected for all devices, except for BiStim^2 which was evaluated with monophasic magnetic pulses.

3. Results

Table 1 summarizes the exactness and precision errors for TMS devices and simulated pulses. All parameters assessed from simulated data showed errors below 5%, with maximum exactness error of 1.6% in spTMS amplitude, and maximum precision error of 1.9% in ppTMS amplitude. Exactness and precision errors for simulated ppTMS ISI and rTMS frequency were smaller than 0.2%.

Exactness errors calculated for each nominal intensity in spTMS protocols revealed that Magpro Compact showed errors of 5.5% at nominal intensity of 90%, Neuro-MS showed an error of 5.51% at 50% of nominal intensity, and Neuro-MS/A showed an error of -7.5% in both 20% and 30% intensities (Table 2-SR). In turn, precision errors were lower than 5% for all intensities. All other devices showed exactness and precision errors smaller than 5%.

Exactness and precision errors in amplitude measurements for rTMS in Table 1 are relative to the maximum stimulation frequency recommended by manufacturers to operate at the maximum intensity (10 Hz for Magpro X100 and 5 Hz for Neurosoft devices, Table 3 – SR). Magpro X100 and Neuro-MS/D showed exactness error higher than 5% for the amplitude. Fig. 1A shows that the measured amplitude decreased significantly for stimulation frequencies higher than 10 Hz, for all stimulators. Ultimately, the measured frequencies for Neuro-MS/A showed exactness errors of 6.92% and 47% in nominal frequencies of 1 Hz and 15 Hz, respectively, with mean experimental values of 0.930 ± 0.01 Hz and 7.9 ± 0.1 Hz. All other devices provided the expected stimulation frequency, evidenced by errors smaller than 0.6%. Plots of measured versus experimental stimulation frequencies are illustrated in Fig. 1B.

Characterization analysis: Magnetic field strength ranged from 1 to 1.3 T for all devices. Rise times for Neurosoft devices ranged from 2.9 to 4.1 μs and MagVenture from 0.9 to 1 μs. Pulse duration ranged from 247 to 317 μs considering all devices (Table 1 – SR). In simulated data, the 100-μs and 300-μs spTMS pulses had an amplitude of 0.506 ± 0.008 V, mean duration of 101.9 ± 0.6 μs and 302.9 ± 3.3 μs, and mean rise time of 26.1 ± 1.1 μs and 72.1 ± 2.8 μs, respectively. Detailed results for each TMS protocol, pulse waveforms, manufacturer's information, and experimental versus nominal intensities plots for all TMS protocols are provided in the Supplementary Results.

4. Discussion

In this study, we developed and validated a method to assess the possible mismatch between nominal and experimental amplitude, ISI and ITI of TMS devices operating in spTMS, ppTMS, and rTMS protocols. The method was validated using sine pulses from a function generator. In addition, we performed the mismatch analysis of six commercial TMS devices, and we characterized the magnetic pulse waveforms, estimating their magnetic field amplitude, the rise time, and pulse duration.

Previous studies comparing TMS pulse parameters between multiple devices and coil configurations already addressed the question regarding changes in the induced electric field (Nieminen et al., 2015; Thielscher and Kammer, 2004). Specifically, Nieminen et al. (2015) developed a device to map and assess the amplitude and focality of TMS coils induced electric field in a spherical head model. However, to our knowledge, the mismatch between nominal and experimental values of TMS protocols has never been evaluated across multiple devices.

In rTMS protocols, the TMS devices might not be able to provide the correct intensities in a high-frequency mode. This is explained by a limitation in the electronic system, in which capacitors might not be able to recharge in time to deliver two consecutive pulses within a short time interval, as shown in Fig. 1C. Indeed, many manufacturers provide the trade-off between rTMS frequency and amplitude in their user guide. Moreover, several manufacturers produce extra recharge modules for use in rTMS protocols to minimize the loss in stimulation intensity. Therefore, devices operating with a recharge module such as Magpro X100 should maintain the desired amplitude at higher frequencies than those without it, such as Neuro-MS, Neuro-MS/A, and Neuro-MS/D.

Even with manufacturers providing information about maximum intensity for each stimulation frequency, depreciation of electronic components in TMS stimulators might occur after extended usage times and therefore lead to variations in adjusted protocols parameters. In this study, Magpro X100 and Neuro-MS/D presented exactness errors higher than 5% even for rTMS parameters certified by the manufacturers. In this case, a good approach to define the maximum recommended amplitude that a given device can operate at a specific frequency might be to estimate the maximum amplitude at which exactness and precision errors are below the proposed 5% limit (Table 3–SR and 4 – SR), providing an independent analysis of the working range for each device and gathering performance information for TMS operators.

Besides, the control design in TMS devices may contribute to possible mismatches in parameters adjustment. For instance, the Neuro

Table 1
Exactness (E) and precision (P) errors of TMS parameters for each device in spTMS, ppTMS, and rTMS protocols.

Device	Maximum magnetic field (T)	spTMS				ppTMS		rTMS					
		Amplitude		Amplitude		ISI		Amplitude*		Frequency*		ITI	
		$\bar{E}$ (%)	$\bar{P}$ (%)	E (%)	P (%)	E (%)	P (%)	E (%)	P (%)	E (%)	P (%)	E (%)	P (%)
Simulated 100 µs	–	1.6	1.3	0.06	1.8	0.05	0.04	0.2	1.7	$< 10^{-3}$	0.003	–	–
Simulated 300 µs	–	0.6	1.5	0.02	1.9	0.05	0.2	0.2	1.7	$< 10^{-3}$	0.007	–	–
Bistim[2]	1.28 ± 0.01	2.8	2.3	2.8	2.3	0.6	0.9	–	–	–	–	–	–
Magpro Comp	1.22 ± 0.01	2.7	1.7	–	–	–	–	–	–	–	–	–	–
Magpro X100	1.34 ± 0.01	1.3	1.5	2.0	1.9	1.8	0.3	**−11.2**	4.3	$< 10^{-3}$	$< 10^{-3}$	2.0	$< 10^{-3}$
Neuro-MS	0.89 ± 0.04	3.7	1.0	–	–	–	–	−0.13	1.6	0.3	0.01	0.8	$< 10^{-3}$
Neuro-MS/A	1.08 ± 0.03	3.8	1.0	–	–	–	–	−0.27	0.7	**−39**	0.28	–	–
Neuro-MS/D	1.01 ± 0.02	1.6	2.1	–	–	–	–	**−12.3**	3.4	0.04	0.02	–	–

*Calculated with the nominal amplitude of 100% and rTMS frequency of 5 Hz (Neuro-MS, Neuro-MS/A, Neuro-MS/D) and 10 Hz (Magpro X100). Precision and exactness errors higher than 5% were considered unsuitable for administration of TMS and highlighted in bold.
$\bar{E}$ and $\bar{P}$ were calculated as the average absolute exactness and precision errors for all nominal amplitudes (spTMS, ppTMS) and ISI (ppTMS).
spTMS: single pulse TMS; ppTMS: paired-pulse TMS; rTMS: repetitive TMS; ISI: inter-stimulus interval; ITI: inter-train interval.

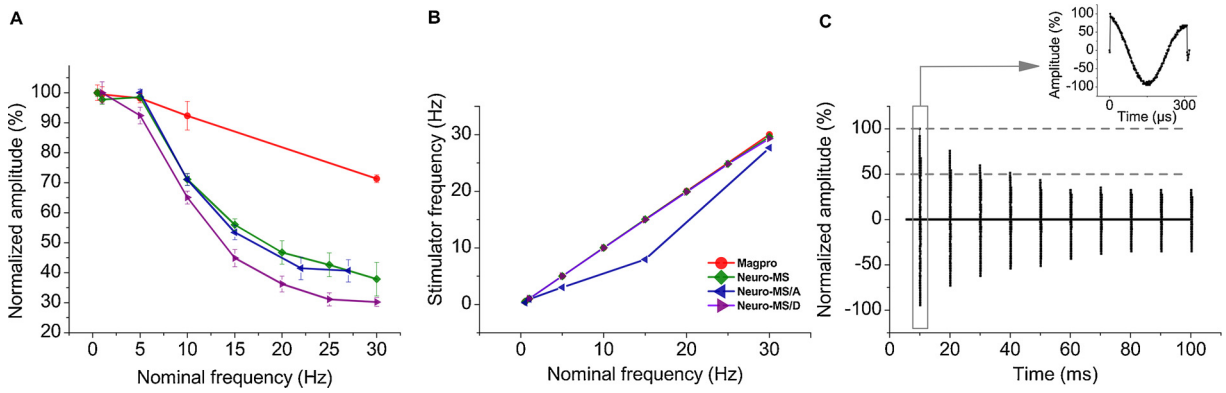

Fig. 1. A) Mean and standard deviation of the last five pulses in a ten-pulse train, with nominal amplitude fixed at 100% and rTMS frequency varying from 0.5 to 30 Hz, representing the dependency of the maximum stable pulse amplitude with the rTMS frequency. Each line and color represent a different device. (B) Mean and standard deviation of stimulation frequencies measured relative to their nominal frequencies with nominal amplitude fixed at 50%. Each line and color represent a different device (C) Representative pulse train at 100 Hz and 100% of stimulation intensity for Magpro X100. Dashed lines represent 100% and 50% amplitudes for reference. Inset plot shows the EMF waveform of the first magnetic pulse of the train.

MS/A showed high errors in exactness and low in precision. One possible explanation is that the analogic knobs used by the operator to control the parameters might have led to parallax errors during parameters adjustment. Even though Neuro-MS/A is no longer produced, this observation still highlights the importance of evaluating the device's quality to prevent undesirable adjustment of parameters.

With the development of controllable pulse TMS devices (Peterchev et al., 2014), several studies are now investigating the effects of timing properties of TMS pulses on biological responses (Koponen et al., 2018). For instance, changing pulse duration increase, or decrease cortical excitability by recruiting different cortical circuits (Hannah and Rothwell, 2017; Rothkegel et al., 2010). Moreover, small variations in rTMS frequency, from 10 to 9 Hz, potentially lead to differential effects on depression treatments (Arns et al., 2010). Thus, our method allows one to assess the variability in the timing properties of TMS devices and offers a simple way to control the parameters in all protocols applications.

In addition to the mismatch analysis, we characterized the strength of the magnetic field, pulse rise time, duration, and waveform across different devices with various electronic configurations. Previous studies showed that these parameters might lead to differences in the induced electric field (Nieminen et al., 2015; Thielscher and Kammer, 2004), and therefore may bias physiological measurements, such as the stimulus-response curves (Arns et al., 2010; Cash et al., 2017; Du et al., 2014; Hannah and Rothwell, 2017; Sommer et al., 2006). In this sense, TMS operators must be aware of possible differences between devices for adequate comparison between studies using different equipment and stimulation protocols. Thus, the pulse characterization analysis provides experimental evidence to control and report the variability of TMS devices in both clinical and research environments.

Finally, the proposed method allows users to verify the device performance immediately before the TMS application. It is necessary to ensure the correct positioning of the search coil in every measurement to monitor the devices over time, for example using a three-axis positioner or a round lid that attaches to the center of one of the coil windings. It is important to highlight that our study was performed in a limited set of TMS devices, which had different workloads. Thus, we did not have a precise information about possible degradation of electronic components. Notwithstanding, we showed that pulse parameters deviate from nominal values, which possibly influence TMS physiological outcomes and equivalence between different studies. Furthermore, the method proposed in this study offers an independent measurement technique to assess the working range of TMS stimulators and can be easily applied to any TMS device. Further experiments should control for usage time and comprise stimulators from other manufacturers, such as Nexstim (Nexstim Oy, Finland), Neuronetics (Neurostar, EUA) and Magstim Rapid[2] (The Magstim Company Limited, UK).

5. Conclusion

The method presented in this study allows the assessment of mismatch between nominal and experimental measurements of TMS

magnetic pulse amplitude and timing properties. Exactness and precision errors indicated that device performance in spTMS and rTMS protocols might deviate from manufacturer's specifications. As expected, all the assessed stimulators were not able to sustain the nominal stimulation intensity at rTMS frequencies higher than 5 Hz. In conclusion, our study proposes a simple method to describe the performance of any TMS device in multiple stimulation protocols, providing the means to account for the influence of different stimulators on the physiological outcomes in research and clinical applications.

Conflict of interest

The authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jneumeth.2019.03.021.

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