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Editorial

Towards more reliable TMS studies – How fast can we probe cortical excitability?

The reliability of TMS effects both within and among studies is one of the most problematic issues for TMS research and clinical use. The most important factor for TMS effects is the stimulation intensity (SI). SI defines TMS effect size (Pellegrini et al., 2018, van de Ruit and Grey, 2016, Nazarova et al., 2021a, Raffin et al., 2020, Padberg et al., 2002), TMS spatial resolution (Mutanen et al., 2021), and TMS safety limits (Rossi et al., 2021). SI is usually adjusted using "resting motor threshold" (RMT) (also called cortical motor threshold), classically defined as a minimal intensity needed to induce a motor evoked potential (MEP) in a relaxed muscle in 50% of the stimuli applied to the contralateral motor cortex (Rossini et al. 2015). RMT is currently used for SI determination in motor and the majority of non-motor TMS applications (Turi et al., 2021). Apart from scaling TMS effects, which were shown for MEP amplitude (Pellegrini et al., 2018), muscle cortical representation area (van de Ruit and Grey, 2016), and clinical effects (Padberg et al., 2002), there may also be a non-linear influence of the RMT. For example, in a large-scale TMS sample from multiple studies, RMT predicted short-interval intracortical inhibition and facilitation effects (Corp et al., 2021). Thus, TMS effects' reliability is greatly based upon RMT determination and its reliability.

Most authors are reporting good to excellent relative reliability of RMT (Beaulieu et al., 2017). At the same time, the absolute reliability of RMT varies greatly among studies (Beaulieu et al., 2017): from the smallest detectable change of 1.1 % for abductor pollicis brevis (Nazarova et al., 2021b) to 16.4% for the deltoid muscle (Tedesco Triccas et al., 2018). Strikingly, in a recent retrospective study of 374 patients from a therapeutic TMS depression program (Cotovio et al., 2021) RMT changed more than 5% from day to day in almost half of the sessions.

RMT search consists of two major steps: (1) hotspot hunting and (2) RMT intensity selection at this hotspot. For the first step of the process - hotspot hunting (sometimes also called "rough mapping" (Krieg et al., 2017; Nazarova et al., 2021b) the following key factors may vary: intensity used for rough mapping, the number of stimuli, the order of the stimuli applied along the cortex and the timing of this process. The intensity used for hotspot hunting is commonly based on expert agreement. For example, in IFCN TMS diagnostic guide (mostly oriented on non-navigated TMS) the recommended SI is the one which results in MEPs with peak-to-peak amplitudes of 500–1000 μV (Groppa et al., 2012), for MRI navigated TMS, lower SI leading to MEPs with peak-to-peak amplitude of 100–500 μV was recommended (Krieg et al., 2017), other approaches with stimulation beginning with the minimal SI, which is gradually increasing, are also used (for instance, Sankarasubramanian et al., 2015). The next factor, the amount of stimuli used for hotspot hunting, is rarely reported in TMS research, but when it is, it is around several tens of stimuli (Sollmann et al., 2013; Tervo et al., 2020). There were recent advances in the hotspot hunting step, aimed to automatize the process of the location (Harquel et al., 2017; Meincke et al., 2016) or both location and orientation target choice (Tervo et al., 2020). However, it is worth mentioning that even in case of a hotspot defined by a comprehensive mapping (≥170 points), the fluctuations of hotspot position between two TMS sessions separated by a week, are up to 1 cm (Nazarova et al., 2021b). The second step of RMT search is RMT intensity selection. While the semi-automatized adaptive option for RMT intensity selection was introduced more than a decade ago (Awiszus, 2003), the manual relative frequency approach (aka Rossini-Rothwell (Rossini et al., 2015)) is still widely used (Turi et al., 2021), and no clear difference between these approaches and their modifications was reported so far (Groppa et al., 2012).

One important aspect, which is commonly overlooked during RMT search, is the interstimulus interval (ISI) choice. While during the main TMS procedure, such as TMS mapping or paired-pulse TMS, the ISIs are usually reported, during RMT search steps – rough mapping and RMT intensity selection - ISIs are rarely indicated. We consider this a problem, as it has been already demonstrated that MEP amplitudes can increase when increasing the ISIs up to 15 s (Hassanzahraee et al., 2019). The work of Kallioniemi et al. (2022) in this issue of *Clinical Neurophysiology Practice* was dedicated to this generally overlooked problem with the effort to compare cortical excitability in the motor cortex using Rossini-Rothwell (Rossini et al., 2015) and threshold-hunting (Awiszus, 2003) approaches with ISIs longer than 5 s and using stimulus–response curves (SRC) with shorter ISIs: 1.2–2, 2–3 and 3–4 s. SRCs were investigated using 108 stimuli. The authors showed that at the individual level, the MEP amplitudes in SRCs were highly affected by the ISIs. Interestingly, there was no trend, which ISI led to bigger MEP amplitudes, as it varied among subjects. The study of Kallioniemi et al. highlights the importance of considering ISIs while interpreting cortical excitability measures in TMS, and indicates the need for further studies to answer questions of

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whether excitability dependence on ISI is individually specific, and what is the optimal ISI for cortical excitability probing.

What can be recommended knowing the findings of Kallioniemi et al.? Above all, we suppose that all the details of the RMT search should be reported to make easier the process of studies meta-analysing and replication. Not only the method of RMT intensity selection but also ISIs used during RMT search steps should be clearly indicated in TMS papers. Another practical consideration is that ISIs, which are sometimes set as the default in TMS machines, should not be too short (at least not shorter than 5 s). Finally, we suppose that the issue of ISIs may be extrapolated to the intensity adjustment other than RMT search, for example, for TMS-EEG based excitability probing or for region-specific threshold assessment such as, for instance, phosphene threshold determination.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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