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Test–retest reliability of single and paired pulse transcranial magnetic stimulation parameters in healthy subjects

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ABSTRACT

Objective: To determine the influence of different factors on test–retest reliability of frequently used transcranial magnetic stimulation (TMS) parameters while controlling for potential confounders in healthy subjects.
Methods: TMS was applied in 93 healthy volunteers (61% male) twice (mean retest interval of 34.0 ± 25.6 (SD) days) between 7 am and 2 pm by four investigators (sessions n investigator A = 47, investigator B = 95, investigator C = 28, investigator D = 16). Women were assessed in their follicular phase. Test stimulus (TS), resting motor threshold (RMT), short latency intracortical inhibition (SICI), intracortical facilitation (ICF) and cortical silent period (SCP) were analyzed.
Results: Good test–retest reliabilities were observed for TS (r = .880) and RMT (r = .826), moderate for visual and automated analyzed CSP durations (resp. r = .466, r = .486), and poor for ICF (r = −.159). Reliable change indexes are reported. Gender (e.g. automated CSP women: r = .538 vs. men: r = .422), re-test interval and method of CSP-analysis did not influence reliabilities.
Conclusions: In a large sample of healthy volunteers we found good to moderate test–retest reliabilities in all but one TMS-parameter. Automated analysis of the CSP did not prove to be more reliable than visual determination.
Significance: This study contains analyses of re-test reliability in TMS considering several confounding factors. For the first time it presents reliable change indices for all frequently used TMS parameters.

1. Introduction

Cortical excitability is frequently assessed using transcranial magnetic stimulation (TMS) for clinical and research purposes [39]. However, to allow the detection of relevant and clinically meaningful changes in TMS parameters and thus cortical excitability following an intervention, sufficient test–retest reliability is required. Confounding factors that may systematically influence TMS results and hence reduce reliability should be recognized and considered when developing TMS-based research protocols.

Several studies have looked at variability in TMS before. Those studies have found overall good reliabilities of TMS parameters in single and paired-pulse settings in healthy volunteers [4,7,14,24] as well as in stroke patients [5,48] and amputees [19].

Resting motor threshold (RMT) was commonly found to be very reliable [4,25,26,35] with few contradictory results [11]. The RMT is defined as excitability of cortico-cortical axons and their connection to pyramidal cells [51] and mainly mediated by voltage-gated sodium channels.

Studies regarding reliability of the cortical silent period (CSP) are sparse [4,14,41]. CSP, here measured as contralateral interruption of tonic contractions of the hand muscle, represents both spinal inhibitory processes during the first 50 ms and cortical mechanisms including motor cortex inhibition later than 100 ms [50]. The latter is thought to reflect inhibition of pyramidal cell $GABA_B$ receptors through interneurons [47,51,52].

Studies on reliability of short latency intracortical inhibition (SICI) and facilitation (ICF) have been inconclusive [2,24,30,46]. Both SICI and ICF are measured using a paired-pulse design. A subthreshold conditioning stimulus (CS) is followed by the suprathreshold individual test stimulus (TS) with varying interstimulus intervals (ISI). ICF can be

Abbreviations: CSP, Cortical silent period; EMG, Electromyography; GABA, Gamma-aminobutyric acid; ICF, Intracortical facilitation; ISI, Interstimulus interval; MEP, Motor evoked potencial; NMDAR, N-methyl-d-aspartate receptor; RMT, Resting motor threshold; RCI, Reliable change index; SICI, Short intracortical inhibition; TMS, Transcranial magnetic stimulation; TS, Test stimulus.

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elicited with ISI of 6–25 ms while SICI is elicited at 1–6 ms [37]. Both, SICI and ICF prove intracortical excitability. Yet, they probably depend on different mechanisms. Both seem to be altered by GABAA dependent inhibition while ICF also responds to NMDAR changes [45].

The variability in TMS parameters might stem from inherent differences between participants [6,26]. In women, TMS has revealed that menstrual cycle phase affects cortical excitability and inhibition [6,18,43]. However, only few TMS studies on retest-reliability included women [9,11,24,42] and only one specified the phase of the menstrual cycle during which TMS was performed [42]. De Gennaro et al. [11] argued that low reliabilities reported were not result of including women as the male participant also showed low reliabilities. Additionally, investigators' skill and expertise in neurophysiological research were suggested to be relevant [4], but investigator effects have not yet been formally studied.

Lately, the proposed method of choice for determination of the CSP duration has been automated computer analysis rather than visual analysis to reduce variability [10,15,21]. Yet, to the best of our knowledge, there is no study comparing both methods regarding test–retest reliabilities, hence no superiority claim can be made.

Moreover, studies on retest reliability have discussed several factors potentially influencing measures of cortical excitability, including age, daytime, handedness [9,24,26,34,36,41,46] and period of menstrual cycle in women [17,18,43].

We therefore chose to control for these latter factors: age by including only young adults, daytime by measuring only during the morning, handedness by only including right-handed individuals and menstrual cycle by measuring during the follicular phase to yield precise data on our main aim on retest reliability. Reliable change indices have not been reported in such a big sample, yet, they are relevant for evaluation of data despite group significance according to their clinical importance.

Based on the pertinent literature we hypothesized, that retest reliability would be strong for RMT and CSP and moderate for SICI and ICF. Furthermore, that automated analysis of CSP would yield higher reliabilities than visually determined CSP and that gender effects on reliability would be absent due to the restrictions in assessing TMS parameters in women.

2. Experimental procedures

2.1. Subjects

Exclusion criteria involved a history of neurological and/or psychiatric disease and use of central nervous system active drugs. Only right-handed subjects with a score ≥80 on the Edinburgh handedness inventory [31] were included to have a homogenous sample for stimulation site, namely only the suspected dominant left hemisphere. Participants consented to refrain from caffeine intake or smoking for 12 h prior to and during assessments. Female participants underwent both TMS sessions during the follicular phase as determined by individual calendars. They were instructed during the screening how regularity of the cycle and follicular phase was defined. They individually determined their follicular phase and contacted the investigators accordingly.

The study conformed to the declaration of Helsinki and was approved by the local ethics committee of the Philipps-University Marburg, Germany. Written informed consent was obtained from all participants.

Ninety-six participants were included in the study. After excluding three participants (one due to technical problems, two did not finish the study) results from 93 volunteers (female n = 36, 38.7%; male n = 57, 61.3%, age: 23.74 ± 3.38 years, range: 19–36 years) were analyzed.

2.2. Investigators

Four investigators applied TMS in this study due to organizational reasons (sessions n investigator A = 47, investigator B = 95, investigator C = 28, investigator D = 16). All investigators received training by two experienced supervisors. For training purposes, all investigators applied TMS and analyzed data of several volunteers before they acquired data for the present study. Throughout the whole study, one experienced investigator was always available for support.

2.3. Sessions

Each participant completed two sessions (T1, T2). These were conducted at minimum of 14 days apart. TMS was repeated on average 34.0 ± 25.6 days after the first session (range 14–173 days). The two sessions represent baseline measurements for an experimental study on carbamazepine induced acute changes of cortical excitability that was published elsewhere [28]. All participants were assessed between 7 am and 2 pm. On average, the second session started 30 min earlier than the first (10:19 h ± 1.26 h vs. 9:49 h ± 1:21 h, p = .005).

2.4. Transcranial magnetic stimulation

Subjects were comfortably seated in an armchair with the head fixed in a custom plastic foam headrest. TMS was delivered through a focal figure-of-eight shaped magnetic coil (70 mm external loop diameter) connected to two Magstim 200 magnetic stimulators via a BiStim-module (all Magstim, Whitland, Dyfed, UK). The coil was placed flat on the head over the left motor cortex, at an approximate angle of 45° to the sagittal plane, inducing a current in the brain roughly perpendicular to the central sulcus, flowing from posterior to anterior, as this has been reported to be the most effective way to activate the corticospinal system transsynaptically [3]. Motor evoked potentials were recorded using surface EMG Ag/AgCl electrodes placed over the right abductor digiti minimi muscle (ADM) in a belly-tendon montage. The raw signal was amplified, filtered (20 Hz–10 kHz) and recorded with a PC using a commercially available data-collection and averaging program (Magnetix®, Center of Sensorimotor Research, Munich, Germany) for offline analysis. The optimal coil placement was determined by recording motor evoked potentials (MEP) while varying the coil position. The coil position leading to the highest peak-to-peak amplitude of the MEP ('hot spot') was marked with a semi-permanent pen directly on the scalp to ensure accurate coil positioning throughout the testing.

All sessions followed a fixed sequence of TMS measurements: First, TS and RMT, then the paired-pulse parameters, SICI and ICF, were obtained in random order. In all paired pulse TMS procedures, the interval between trials was randomly changed between 4 and 6 s, in single pulse procedures the inter-trial interval was 5 s. The protocol concluded with determination of the CSP.

2.5. TMS-parameters

TMS is a well-known non-invasive stimulation technique and it was applied ensuring high standards [13,33]. The parameters were specified as follows:

1. The resting motor threshold (RMT) was defined as the lowest stimulator output intensity that induced MEP peak-to-peak amplitude greater than 50 μV in at least five of ten consecutive trials. Complete muscle relaxation was monitored via audiovisual feedback. A step-by-step intensity resolution of the maximal stimulator output was used for determination of the individual RMT using the maximum likelihood threshold hunting (MLTH) procedure for TMS (Friedemann Awiszus, Magdeburg [1]).
2. Short intracortical inhibition (SICI) and intracortical facilitation (ICF) were obtained with paired-pulse TMS. A conditioning and a test stimuli were applied with different fixed interstimulus intervals (ISI). The conditioning stimulus was set to an intensity of 75% of the RMT as this does not produce changes of excitability in the spinal