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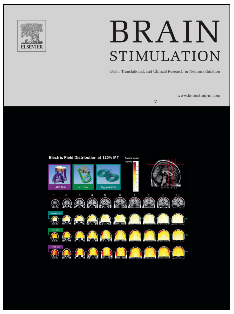

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Reliability of single and paired pulse transcranial magnetic stimulation parameters across eight testing sessions

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Dear Editor,

Transcranial magnetic stimulation (TMS) is a popular method for measuring motor cortical excitability in healthy and clinical populations, and is often used as an outcome measure to explore changes following an intervention. It is therefore important that the reliability of these measures is extensively examined and demonstrated. Several studies have sought to explore this [1-5], and have typically included assessment of reliability across 2-3 sessions for the following measures: motor threshold (MT); TMS recruitment/input output (IO) curves; short interval intracortical inhibition (SICI); and intracortical facilitation (ICF). These have revealed varying degrees of reliability across the different parameters [6]. Here we report the results of an in-depth exploration of TMS measures over an extensive testing period of 8 sessions. We also explore the impact of different data analysis processes.

Ten right handed individuals who did not smoke or have a history of neuro/psychiatric illness participated (7 female, mean age 24 ± 4 years). Each participant completed 8 sessions, which were conducted in two blocks of four. Within blocks, each session was typically separated by 3-4 days (maximum interval 8 days) and an average of 181.8 days elapsed between the two blocks of testing. The time of day when testing was conducted was kept approximately constant within participants. Ethical approval was granted by the School of Psychology ethics committee, University of Nottingham.

TMS was delivered using a BiStim TMS system (Magstim, Dyfed, UK) with a figure-of-8 coil (70mm). Neuro-navigation software (Brainsight, Rogue Research Inc., Montreal, Canada) was used in conjunction with each participant’s anatomical brain scan to aid accurate coil placement over the hand area of the left primary motor cortex (M1). MEP recording and general TMS administration were identical to our previous study [7]. Resting motor threshold (RMT) and 1mV threshold (SI1mV) were measured using established procedures. IO curves were measured using TMS intensities set at 100, 110, 120, 130, 140 and 150% of RMT. Ten pulses at each of the six intensities were delivered in a randomized order, with 5 second inter stimulus intervals (ISI). The following paired pulse protocols were measured: ***1ms SICI*** (Condition stimulus (CS) intensities of 45, 50, 55, 60% RMT); ***3ms SICI*** (CS 60, 65, 70 or 75% RMT) and ***10ms ICF*** (CS 65, 70 or 75% RMT). The test stimulus (TS) for paired pulse measures was set at SI1mV. Each CS-TS pairing was measured 10 times for each protocol. A total of 30 unconditioned trials were also measured at SI 1mV.

IO curve measurements were derived by calculating the median intra-individual MEP amplitudes for each TMS intensity value (i.e. 100-150% of RMT); linear fits were then applied to the resultant values (mean R^2 = 0.89). Paired pulse data was analysed by normalizing both mean and median MEP amplitudes evoked from conditioned trials to the respective mean/median of unconditioned trials. To account for individual differences in patterns of response, and limit floor effects (due to total abolishment of MEP in some SICI measures), intra-subject median/mean inhibition or facilitation across the various CS intensities was calculated (e.g. average inhibition caused by CS intensities of 45, 50, 55 and 60 in the 1ms SICI condition). Grubbs test (with a α level of .01) detected a single outlier for session 5 of the 3ms SICI measure. This was removed prior to further analysis.

A repeated measures ANOVA revealed a significant main effect ($F(2,16)=44.51$, p=.000, η_p^2 =.848) of TMS measure (1msSICI, 3ms SICI, 10ms ICF), but no significant main effect ($F(1,8)$=.1.745, p=.223, η_p^2=.179) of analysis type (mean/median) or session ($F(7,56)$=1.707,p=.126, η_p^2=.176. A significant interaction between analysis type and TMS measure was found $F(2,16)$=10.075, p=.001, η_p^2=.557,), hence all reliability measures are reported using both methods of averaging. Intra-class correlation coefficient (ICC (2,1)) analysis was used to explore the reliability of the different TMS measures. This was tested for each of the two blocks separately and combined. The ICC results are reported based upon Lahey, Downey [8] which defines intra-class variability as poor if values are <0.4, fair if >0.4 and <0.59, good if >0.6 and <0.74 and excellent if values are >0.74. Pearson's correlations were also calculated between testing sessions for each measure to allow for comparison to previous work [2, 3].

Repeated measure ANOVA's established no significant differences between RMT (F(7,63)=1.469, p=.195, η_p^2=.14) and SI1mV (F(7,63)=1.85, p=.988, η_p^2=.02) across testing sessions. The results of ICC and Pearson's correlations can be seen in Table 1. In summary, all RMT (ICC(2,1) => 0.923), all SI1mV (ICC(2,1)=> 0.892) and all IO curve slope (ICC(2,1) => 0.807) analyses were found to show excellent reliability when assess by block and across 8 testing sessions combined. These results confirm the findings of previous studies with fewer sessions [1-3]. Interestingly, correlations between sessions separated by a number of months (sessions 4 and 5), showed no clear differences relative to correlations obtained for sessions separated by 3-4 days (data not shown), suggesting stability in RMT and IO curve measures over sustained time periods.

Reliability for 1ms SICI varied depending on the analysis used (i.e., mean vs. median) and sessions analysed (block 1, 2, or combined) from poor (ICC(2,1) = 0.261) to good (ICC(2,1) = 0.613). Whereas, 3ms SICI showed fair reliability at worst (ICC(2,1) = 0.488) and excellent reliability (ICC(2,1) = 0.870) at best. The moderate-good levels of reliability found for the 3ms SICI condition largely supports findings of recent studies using subtly different methodology [1, 2]. Although Maeda et al [3] reported good reliability between two sessions, for both 1ms SICI and 3ms SICI. It is possible that the 1ms SICI discrepancy is due to differences in the methods: in particular the CS intensities used and our decision to average across CS intensities.

10ms ICF was found to have poor-fair reliability which was influenced by the choice of averaging (mean/median). Consistent with previous reports, it was the least reliable of the measures we assessed [2-4].

Overall, we demonstrate excellent reliability for commonly-used single pulse TMS measures and fair-to-excellent reliability for 1ms and 3mc SICI whether assessed across days or across a six months internal.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Table caption:

Table 1. ICC values calculated using data from the first four (Block 1), the last four (Block2) or across all testing sessions. **excellent, * good & †fair reliability. Min/max values derived from Pearson’s correlations showing amount reaching levels of significance at p=<.005 and after Bonferroni adjustment.

	ICC(2,1)			Pearson's R			
	Block 1 Day 1-4	Block 2 Day 5-8	All Day 1-8	Maximum Day1-8	Minimum Day 1-8	Total *p*=<0.05	Bf corrected p=<.007
RMT	.983**	.974**	.923**	r=.990, *p*=.000	r=.809, *p*=.005	28/28	28/28
SI1mV	.981**	.991**	.892**	*r*=.991, *p*=.000	r=.838, p=.002	28/28	28/28
IO Slope	.923**	.862**	.807**	r=.955, *p*=.000	r=.595, *p*=.070	25/28	18/28
1ms SICI median	.261	.495†	.422†	r=.801, *p*=.005	r=.064, *p*=.86	8/28	2/28
1ms SICI mean	.577†	.613*	.561†	r=.842, p=.002	r=.339, p=338	8/28	3/28
3ms SICI median	.488†	*.821***	*.670**	r=.962, *p*=.000	r=.156, *p*=.666	13/28	5/28
3ms SICI mean	.511†	.870**	.745**	r=.957, p=.000	r=.325, p=.360	16/28	13/28
10ms ICF median	.224	.398	.224	r=.777, *p*=.008	r=-.01, *p*=.978	3/28	0/28
10ms ICF mean	.583†	.446†	.448†	r=.862, p=.001	r=.017, p=.964	6/28	3/28