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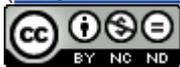
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Journal Title: Neuroscience Letters
Volume: Volume 640
Publisher: Elsevier | 2017-02-15, Pages 47-52
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.neulet.2017.01.032
Permanent URL: <https://pid.emory.edu/ark:/25593/s89g6>

Final published version: <http://dx.doi.org/10.1016/j.neulet.2017.01.032>

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Accessed September 17, 2019 7:35 AM EDT



Published in final edited form as:

Neurosci Lett. 2017 February 15; 640: 47–52. doi:10.1016/j.neulet.2017.01.032.

Establishing between-session reliability of TMS-conditioned soleus H-reflexes

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Abstract

Transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) can be used to evaluate descending corticomotor influences on spinal reflex excitability through modulation of the Hoffman reflex (H-reflex). The purpose of this study was to characterize between-session reliability of cortical, spinal, and cortical-conditioned spinal excitability measures collected from the soleus muscle.

Thirteen able-bodied young adult participants were tested over four sessions. Intraclass correlation coefficients were calculated to quantify between-session reliability of active motor threshold (AMT), unconditioned H-reflexes (expressed as a percentage of M_{max}), and conditioned H-reflexes using short-latency facilitation (SLF) and long-latency facilitation (LLF). Pearson correlation coefficients were calculated to assess associations between H-reflex facilitation and unconditioned H-reflex amplitude.

Between-session reliability for SLF (ICC = .71) was higher than for LLF (ICC = .45), was excellent for AMT (ICC = .95), and was moderate for unconditioned H-reflexes (ICC = .63). Our results suggest moderate-to-good reliability of SLF and LLF to evaluate cortical influences on spinal reflex excitability across multiple testing sessions in able-bodied individuals.

Keywords

TMS; H-reflex; reliability; corticospinal excitability; TMS-conditioning; facilitation

Introduction

Transcranial magnetic stimulation (TMS) of the primary motor cortex (M1) can be used to evaluate descending corticomotor influences on spinal reflex excitability through modulation of the Hoffman reflex (H-reflex) [12, 24]. Sub-threshold TMS conditioning pulses delivered either before or after electrical stimulation of a peripheral nerve [10, 13, 14, 19, 20] cause

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modulation of the H-reflex. Studies investigating the time course of TMS-conditioned H-reflex modulation have demonstrated two sets of interstimulus interval (ISI) ranges that result in H-reflex facilitation to index the excitability of descending neural pathways [10, 20]. Short-latency facilitation (SLF) occurs when TMS is applied 1–5ms *after* peripheral stimulation is delivered and is mediated by a direct, monosynaptic pathway involving corticospinal projections to the soleus spinal motor neuron [20]. On the other hand, long-latency facilitation (LLF) is observed when TMS is delivered 5–10ms *before* peripheral stimulation and is hypothesized to index the excitability of indirect polysynaptic descending pathways involving cortical, brainstem, and/or spinal interneurons to the soleus spinal motor neuron [10, 11].

H-reflex modulation evaluated using SLF and LLF provides a non-invasive mechanistic approach to investigate the integration of cortical and spinal volleys in motor output pathways required for movement production. For example, SLF and LLF of the soleus H-reflex are regulated differently with movement[20]. Therefore, SLF and LLF index the excitability of different descending neural pathways that may be differentially affected by neurological conditions and may recover or respond to treatment differently. By characterizing excitability of corticomotor connections in humans using SLF and LLF, novel neurobiological targets may be identified to promote both cortical and spinal plasticity to improve motor function in neurologic conditions [7, 36]. To further define the psychometric properties of SLF and LLF for future applications in longitudinal study designs evaluating cortical contributions to spinal excitability, the reproducibility of these measures needs to be established. Reliable measures of neurophysiology are particularly important when tracking nervous system changes over time either in response to behavioral experience (e.g. skill learning) or in the context of a disease process (e.g. multiple sclerosis). Further, understanding the range of physiological variability and measurement error can facilitate the interpretation of excitability changes in the pathways indexed by SLF and LLF.

Studies in both upper and lower extremity muscles have demonstrated good-to-excellent between-session reliability for a number of TMS measurements including: motor evoked potential (MEP) amplitude, [3, 4] resting and active motor thresholds (RMT and AMT, respectively) [3, 4, 18], and cortical silent period (CSP) [16, 33]. Excellent reliability has also been reported for soleus H-reflex measures (H_{max} , M_{max} , and H_{max}/M_{max} ratio) [6, 17, 22, 31, 35]. Each of these measures is commonly used to evaluate cortical and spinal excitability changes over time or in response to a given intervention in clinical populations. However, these measures used in isolation provide an incomplete assessment of the neural pathways responsible for producing movement. Including assessments of SLF and LLF with traditional cortical and spinal excitability measures has the potential to better characterize neural substrates of normal and abnormal movement. To our knowledge, the between-session reliability of TMS-conditioned H-reflex measures (e.g. SLF, LLF) has not previously been systematically evaluated. Therefore, the primary purpose of this study was to characterize the between-session reliability of measures of cortical (AMT), spinal (H-reflex), and cortical-conditioned spinal (SLF/LLF) excitability of the soleus muscle in able-bodied participants.

Materials and Methods

Subjects

Thirteen young neurologically-intact participants (age: 26 ± 2.4 years, 10 F) were recruited and completed the experimental protocol. Exclusion criteria included: 1) any known neurologic or orthopedic disorder, 2) outside the age range of 18–35 years old, or 3) contraindications to TMS [29]. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Study procedures were approved by the Emory Institutional Review Board.

Experimental design

Data were collected as part of a larger investigation aimed at evaluating the transient (<1 hour) neurophysiologic effects of different walking bouts (level, upslope, downslope, and split-belt treadmill walking). In the larger study, cortical and spinal excitability measures were collected both before and after the treadmill walking, however, measurements included for the current investigation were collected at the beginning of each session (baseline), prior to the individual walking bout.

Participants completed four experimental sessions separated by a minimum of 24 hours. Study procedures were completed at a similar time of day for each session (within a one-hour window) to avoid potential effects of diurnal variation on neural excitability [5, 37]. Participants were also asked to maintain similar levels of physical activity while enrolled and refrain from caffeine intake for 12 hours before each visit [34]. The right leg was tested in all participants. Measurements were obtained with the participant seated in a semi-recumbent position with the hips and knees at 30° of flexion and the ankle secured in 10° of plantar flexion. The lower extremities were placed in a paired rigid boot and stabilized using inelastic straps, and the distal thighs were stabilized with straps to prevent external hip rotation or abduction.

Electromyography

Following standard skin preparation procedures, bipolar surface EMG electrodes were attached over the right soleus muscle 2cm apart along the posterior lateral aspect of the muscle. A ground electrode was placed over the ipsilateral lateral malleolus. Outlining the electrodes with permanent marker on the skin ensured consistent electrode placement across the four sessions. EMG signals were band-pass filtered (5–1000Hz) and amplified (x2000) using a Biopac EMG system (BN-EMG2, Biopac Systems Inc.).

Volitional muscle activity can influence spinal and cortical excitability measures [2, 30], therefore, right soleus background EMG activity was maintained at a consistent low-level (matched to the level of an individual's voluntary EMG during quiet standing) during data collection. Prior to testing, soleus EMG activity was measured during 30 seconds of quiet standing, and the average rectified activity was recorded. During testing, participants were instructed to contract their soleus muscle by pushing against a foot plate, and visual feedback was provided to maintain their average rectified soleus EMG activity at a target level equal to the EMG amplitude obtained during quiet standing [31].

Spinal excitability

H-reflexes were evoked by stimulating the tibial nerve within the popliteal fossa using a monopolar electrode (round, 2.5cm), with the anode (square, 5cm) placed at the midline over the patella [25]. The stimulating electrodes were self-adhering carbon rubber TENS/NMES electrodes (Medical Products Online, Danbury, CT). Sixty single 1-ms duration rectangular pulses were delivered at pseudo-random intervals (5–8 sec inter-pulse interval) using a constant-current electrical stimulator (STMISOLA, Biopac Systems Inc.) that was controlled with custom-written scripts in AcqKnowledge software (Biopac Systems Inc.). To acquire the H-reflex recruitment curve, electrical stimulation intensity was increased in increments of 0.5–1.0mA until maximal H-reflexes (H_{max}) and muscle responses (M_{max}) were obtained, as measured by the peak-to-peak amplitude of the raw EMG signal [31]. An example of an H-reflex/M-wave recruitment curve is illustrated in Figure 1.

TMS

Soleus MEPs were evoked by single TMS pulses delivered with a custom 70mm figure-of-eight batwing coil (Magstim Company Ltd., Dyfed, UK) connected to a monophasic stimulator (Magstim 200²). TMS was delivered over the right soleus motor “hot spot” within the left M1 defined as the optimal coil position to elicit maximal MEP responses in the target muscle [30]. Consistency and accuracy in coil placement over the hot spot within and across sessions was maintained using stereotaxic neuronavigation (Brainsight v. 2.2.14, Rogue Research Inc., Canada). Procedures for obtaining AMT were modified from typical protocols [30]; tonic EMG activity during sustained low-level isometric contraction (10–20% maximum voluntary contraction (MVC) [23] of the soleus was based on the H-reflex procedures [31]. In this study, AMT was determined as the lowest stimulator intensity needed to evoke a soleus MEP of 100 μ V peak-to-peak amplitude in at least 3 out of 5 trials during tonic plantar flexion at a level equal to EMG activity measured during quiet standing.

TMS-conditioning of the H-reflex

To investigate cortical influences on spinal excitability, sub-threshold TMS (90% AMT) was delivered at two different time intervals relative to electrical stimulation of the tibial nerve (Figure 2). To elicit SLF, a TMS pulse was delivered 1.5ms after peripheral stimulation (–1.5ms) [10]. For LLF, a TMS pulse was delivered 10ms prior to peripheral stimulation (+10ms) [19–21]. 10 unconditioned (UC) and 20 conditioned H-reflexes were collected at each ISI at a frequency 0.25Hz. The intensity of tibial nerve stimulation was set to produce unconditioned H-reflex peak-to-peak amplitudes equivalent to 20% of M_{max} , as reflexes of this size have been shown to be sensitive to inhibitory and facilitatory conditioning [8, 10, 20, 24]. If necessary, adjustments to electrical stimulation intensity were made between SLF and LLF measurements to maintain the desired unconditioned H-reflex amplitude. The 10 unconditioned H-reflexes from SLF and LLF measurements were combined to compare equal numbers of conditioned to unconditioned H-reflex responses.

Statistical analysis

For SLF and LLF measurements, a TMS-conditioned H-reflex ratio was calculated and utilized for statistical analysis:

$$\text{TMS- conditioned H- reflex ratio} = \frac{\text{conditioned H- reflex}}{\text{unconditioned H- reflex}}$$

A RM-ANOVA was conducted to calculate intraclass correlation coefficients (ICCs) to quantify between-session reliability of baseline measurements of AMT, unconditioned H-reflexes, and conditioned H-reflexes (SLF and LLF):

$$\text{ICC}(3, 1) = \frac{(\text{BMS} - \text{EMS})}{[\text{BMS} + (k - 1)\text{EMS}]}$$

where BMS = between-subjects mean square; EMS = error mean square; k = the number of comparisons [26]. Although not a primary outcome of interest, reliability of baseline M_{\max} values was assessed since these values were used to determine tibial nerve stimulation intensity during TMS-conditioning of the H-reflex. Additional reliability analyses were performed for secondary measures of peripheral excitability (Table 1). ICC thresholds for describing the level of reliability were as follows: very good/excellent = .81–1.00, good = .61–.80, moderate = .41–.60, fair = .21–.40, and poor = .20 [1]. To assess the relative variation in the dependent measures both between sessions and between participants, median coefficients of variation (CV) were calculated:

$$\text{CV} = \frac{\text{SD}}{\text{Mean}} \times 100$$

where SD = standard deviation [26]. All statistical analyses were performed with SPSS (version 22.0), and statistical comparisons were based on an a priori significance level of $p < 0.05$.

Results

Between-session reliability

Results for the ICC analyses are summarized in Table 1. M_{\max} could not be achieved at one visit for a single participant; therefore, all dependent measures that involve M_{\max} values (UC H-reflex, UC/H_{\max} , H_{\max}/M_{\max} , M_{\max}) for this individual were not included in ICC calculations. An additional participant demonstrated non-physiologic H_{\max}/M_{\max} ratios for all visits, and these values were subsequently removed from ICC and correlation analyses. Briefly, the highest between-session reliability was observed for H_{\max} (ICC = 0.98, $F = 40.711$, $p < 0.001$, $n = 13$), while LLF (ICC = 0.45, $F = 1.81$, $p = 0.084$, $n = 13$) demonstrated the lowest reliability and SLF reliability was in between (ICC = 0.71, $F = 3.43$, $p = 0.002$, $n = 13$). Mean values for dependent measures collected at each study visit are summarized in Table 2.

Relative variation

Median CV values for the dependent measures are summarized in Table 2. The lowest CV between sessions was found for AMT (CV = 4.99%, range: 1.89–11.51%) and H_{\max}/M_{\max}

(CV = 14.14%, range: 4.85–34.26%). The highest between-session CV was observed for UC/H_{max} ratios (CV = 39.59%, range: 24.81–73.88%) and LLF (CV = 37.86%, range: 13.98–68.32). The lowest between-participant CV was determined for AMT (CV = 15.78%, range: 12.55–18.52%) and M_{max} (CV = 29.76%, range: 25.99–39.93%). The largest CV between participants was observed for H_{max} (CV = 61.12%, range: 58.03–65.24%) and UC/H_{max} ratios (CV = 53.45%, range: 43.69–59.76%).

Discussion

The principal finding of this study is that between-session reliability varies for measures of TMS-conditioned H-reflexes across multiple study visits. Overall, TMS-conditioned H-reflexes show moderate to good reliability, with SLF demonstrating superior between-session reliability compared to LLF. Secondly, reliability of cortical excitability and spinal excitability assessments varied across measures with TMS-based AMT showing the highest reliability whereas LLF demonstrated the lowest overall reliability of the measures collected. The measures collected in the current experiments also exhibited different between-session and between-participant variability. These findings are the first to characterize the between-session reliability of TMS-conditioned soleus H-reflex responses in young neurologically-intact individuals.

Here we observed higher between-session reliability for SLF than LLF assessments performed on four separate testing days. One potential explanation for the difference in between-session reliability between the two conditioning paradigms is the proposed neuroanatomical and physiological correlates of SLF and LLF. SLF is thought to be mediated by a monosynaptic pathway involving direct corticospinal projections, while polysynaptic pathways are hypothesized to mediate LLF [20]. These polysynaptic pathways may include corticorubrospinal, reticulospinal, vestibulospinal, and/or tectospinal tracts that can synapse on different populations of spinal neurons, including interneurons and/or lumbar propriospinal neurons [10, 28]. Within the nervous system, each step of synaptic transmission is a source of potential variability that can manifest in subsequent synapses [9, 27]. Therefore, the polysynaptic nature of LLF may result in greater variability (and decreased reliability) in the conditioned H-reflex. In contrast, the sensitivity of SLF to the effects of synaptic variability should be less given SLF is mediated by a monosynaptic pathway, likely resulting in more reliable H-reflex conditioning at a short ISI. A similar phenomenon has been observed with TMS measures of intracortical inhibition and facilitation. Short-interval intracortical inhibition (SICI) is a dual-pulse TMS paradigm in which two TMS pulses are separated by a short interval (1–3ms), while with short-latency intracortical facilitation (ICF), pulses are separated by an interval of 7–15ms. A recent study reported higher ICC values for SICI compared to ICF in healthy older adults [32], suggesting that engaging fewer neural processes with shorter latency ISIs may result in greater reliability. The difference in stability, as measured by relative variation between sessions (Table 2), of these two measures may have implications for designing longitudinal studies aiming to use cortical conditioning of H-reflexes to investigate and/or promote changes in corticospinal plasticity. For example, if the lower reliability of LLF versus SLF is replicated in future studies on larger samples and clinical populations, it could impact sample size calculations for investigations evaluating cortical-facilitation of H-reflexes.

Based on the current findings, changes in LLF across assessments should be interpreted cautiously and further studies are warranted to optimize experimental procedures to improve between-session reliability.

Excellent between-session reliability (ICCs $\geq .80$) was found for AMT, M_{\max} , H_{\max} , and H_{\max}/M_{\max} ratio (Table 1), consistent with ICC values previously reported in the literature. However, reliability for unconditioned H-reflexes in our study was lower than previous reports [3, 17, 22, 31]. One major difference between the current study and previous investigations is the number of experimental sessions. Previous reports focused on trial-to-trial reliability within the same session or between-session reliability for only two sessions. In contrast, our study conducted analysis of between-session reliability using 4 separate testing sessions, which could contribute to additional variability resulting in lower observed reliability. However, an understanding of test-retest reliability across multiple sessions, as reported here, may be valuable for longitudinal studies comprising multiple evaluations over time or over the course of a behavioral intervention. Additionally, the small sample size of our study may also have affected H-reflex reliability, but this is unlikely a primary contributing factor due to comparable sample sizes with previous reliability studies [15, 22]. However, our relative variation results suggest that future H-reflex conditioning studies be conducted with larger sample sizes than evaluated here, as we observed between-participant variation to be greater than between-session variation for most dependent measures (Table 2). These findings underscore the importance of developing methodological guidelines that ensure, firstly, procedural uniformity for eliciting and collecting H-reflexes; and secondly, consistency of the unconditioned H-reflex amplitude at a specified low percentage of M_{\max} (on the ascending limb of the H-reflex recruitment curve) to maximize reliability and stability of H-reflex conditioning paradigms.

The current study has limitations. For example, it was part of a larger repeated-measures crossover design study evaluating the influence of walking on cortical and spinal excitability. Although there is a possibility that baseline measures for the second through fourth visits were affected by walking during the previous session, we found no evidence of lasting effects of walking bouts on excitability in a previous study [31]. Moreover, a 24-hour washout period was chosen a priori to minimize any potential confounding effects of persisting modulation of excitability. We also utilized pre-walking assessments for each visit to avoid any potential within-session confounding influences. Another limitation is that multiple experimenters were involved in data collection; however, this is unlikely to be a significant limitation given most excitability measures (e.g. AMT, H_{\max}) collected by these experimenters demonstrated high between-session reliability. Additionally, evaluating LLF and SLF using a greater number of trials could improve the reliability of these measures, and may be an important methodological consideration for future studies. Although electrical stimulation intensity was adjusted and monitored during testing to maintain the desired unconditioned H-reflex amplitude, more rigorous monitoring and adjustment may improve the reliability of unconditioned H-reflex responses. Lastly, a single ISI for SLF and LLF was chosen a priori due to time constraints associated with the larger study design and were based on previous literature. The intervals selected were not individualized for each participant thus maximal facilitation at each ISI may not have been elicited for each participant. All participants did demonstrate TMS-conditioned facilitation except for one

participant during SLF assessment. Future studies would benefit from individualizing ISIs for each participant to elicit maximal TMS-conditioned responses associated with direct and indirect corticomotorneuronal connections and to account for inter-individual differences that could impact the group-level reliability of SLF and LLF assessments.

In conclusion, SLF and LLF were established as methods to evaluate cortical influences on spinal reflex excitability in healthy participants with moderate-to-good reliability across multiple testing sessions. Normal physiologic variations in cortical and peripheral measures were also reported, which can guide development of future longitudinal studies focused on TMS-conditioning measures. By identifying potential factors that lower LLF reliability, our findings suggest methodological modifications may increase the reliability of LLF that will benefit future investigations employ these measures. Incorporation of TMS-conditioned H-reflexes as additional neurophysiologic measures of experience-dependent neuroplasticity may have the potential to generate novel insights into the mechanisms underlying clinical interventions targeting abnormal movement. Incorporation of TMS-conditioned H-reflexes (SLF and LLF) as outcome measures can supplement measures derived using TMS (motor threshold, MEP recruitment curves, MEP amplitude) or peripheral nerve stimulation alone (H/M ratio, M-max) to better elucidate potential clinical biomarkers to target with clinical interventions.

Acknowledgments

MRB is supported by the National Institute of Child Health and Human Development [grant number K12HD055931] and was supported by the National Institutes of Health [grant number 5R24HD050821-11]. WAG was supported by a postdoctoral fellowship from the National Institute of Neurological Disorders and Stroke [grant number 1U10NS086607]. TMK is supported by the National Institute of Child Health and Human Development [grant number K01 HD079584]. MJS is supported by the National Institutes of Health [grant number HD083727-01A] and the National Multiple Sclerosis Society [PP2321]. We would like to thank James Chen, Collette Wade, Jennifer Walters, and additional lab members for assistance with data collection.

Abbreviations

TMS	transcranial magnetic stimulation
M1	primary motor cortex
H-reflex	Hoffman reflex
AMT	active motor threshold
SLF	short-latency facilitation
LLF	long-latency facilitation
ISI	interstimulus interval
MEP	motor evoked potential
CSP	cortical silent period
RMT	resting motor threshold

UC unconditioned H-reflex

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Highlights

- Intersession reliability of TMS-conditioned spinal excitability measures is assessed.
- Moderate-to-good reliability found for two conditioning paradigms.
- Differences in corticomotorneuronal pathways may explain differences in reliability.
- Methods should be developed to enhance reliability of TMS-conditioning paradigms.
- Established reliability of two indices of cortical influence on spinal excitability.

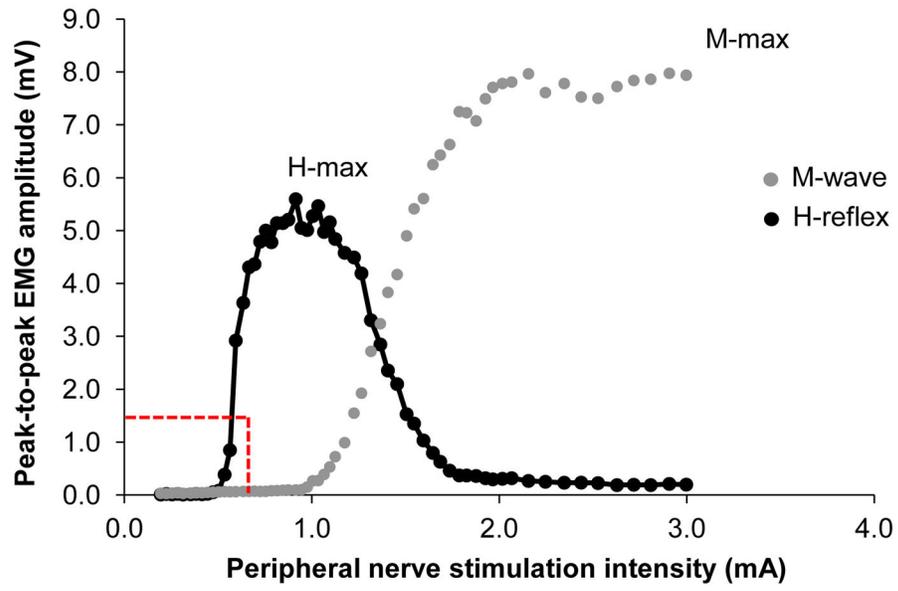


Fig. 1. Example of a H-reflex recruitment curve from a single participant. Red dashed lines mark the stimulation intensity used to elicit unconditioned H-reflexes.

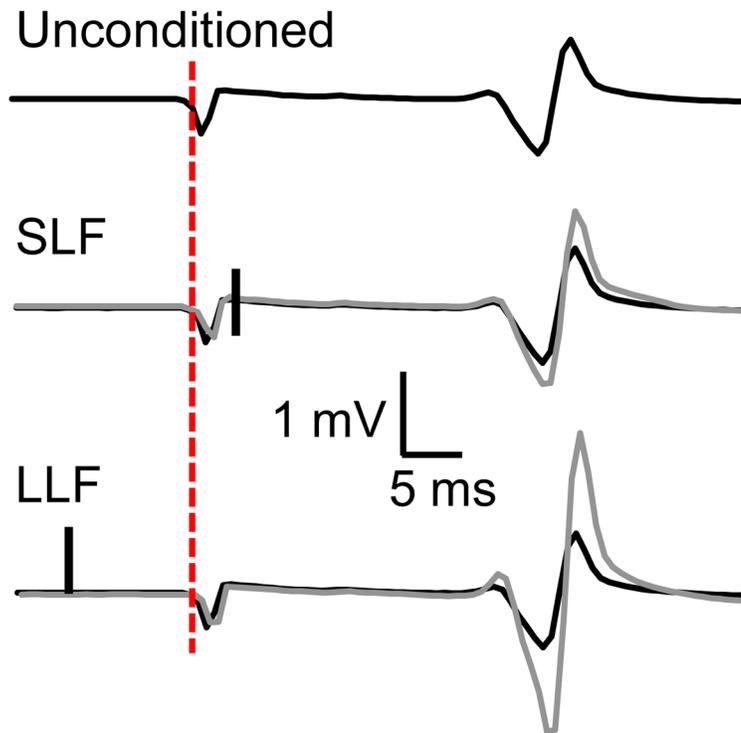


Fig. 2. Raw EMG traces of illustrating TMS-conditioning of the H-reflex from a single participant. Top: average of 20 unconditioned H-reflex responses recorded from the soleus muscle during electrical stimulation of the tibial nerve. Middle: TMS-conditioning of the H-reflex during short-latency facilitation (SLF, ISI: -1.5ms , gray line). Bottom: TMS-conditioning of the H-reflex during long-latency facilitation (LLF, ISI: $+10\text{ms}$, gray line) Red dashed line represents onset of peripheral nerve stimulation, and black solid lines represent TMS delivery over the cortical representation of the soleus. In line with previous research [10, 20], larger TMS-conditioned H-reflexes were observed for LLF compared to SLF (statistical results not reported).

Table 1

Reliability assessments for SLF, LLF, AMT, and secondary peripheral excitability measures

Measure	ICC	p-value	N
SLF	0.71	0.002	13
LLF	0.45	0.084	13
UC	0.63	0.014	12
M_{\max}	0.87	<0.001	12
H_{\max}	0.98	<0.001	13
UC/ H_{\max}	0.70	0.002	12
H_{\max}/M_{\max}	0.95	<0.001	11
AMT	0.95	<0.001	13

SLF: SLF-conditioned H-reflexes (ISI: -1.5ms); LLF: LLF-conditioned H-reflexes (ISI: +10ms); UC: unconditioned H-reflexes; AMT: active motor threshold.

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Table 2
Coefficient of variation (CV) of dependent cortical and spinal measures across sessions and participants.

Dependent Measure	Median CV (%)	Range (%)	Mean(SD) V1	Mean(SD) V2	Mean(SD) V3	Mean(SD) V4
Between-session						
SLF	15.40	5.46–47.32	1.25(0.34)	1.29(0.42)	1.41(0.60)	1.37(0.32)
LLF	37.86	13.98–68.32	2.02(0.77)	2.22(0.89)	3.02(1.55)	2.20(0.94)
UC	34.32	11.87–68.32	0.21(0.09)	0.19(0.10)	0.17(0.09)	0.18(0.08)
M _{max}	17.58	1.33–45.41	6.51(1.83)	6.09(1.91)	5.90(2.36)	6.44(1.67)
H _{max}	16.93	5.41–35.25	4.10(2.39)	3.65(2.33)	3.52(2.29)	3.65(2.11)
UC/H _{max}	39.59	24.81–73.88	0.38(0.17)	0.36(0.29)	0.32(0.19)	0.37(0.19)
H _{max} /M _{max}	14.14	4.85–34.26	0.61(0.25)	0.60(0.25)	0.61(0.29)	0.56(0.26)
AMT	4.99	1.89–11.51	60.0(7.5)	59.4(11.0)	58.6(9.5)	59.5(9.1)
Between-participant						
SLF	29.80	23.31–42.78				
LLF	41.37	37.98–51.37				
UC	50.10	42.09–53.86				
M _{max}	29.76	25.99–39.93				
H _{max}	61.12	58.03–65.24				
UC/H _{max}	53.45	43.69–59.76				
H _{max} /M _{max}	43.84	41.47–47.03				
AMT	15.78	12.55–18.52				

Mean values (standard deviation, SD) are provided for each dependent measure at each visit (V1 - V4)