JYX
JYVÄSKYLÄN YLIOPISTO
UNIVERSITY OF JYVÄSKYLÄ

This is a self-archived version of an original article. This version may differ from the original in pagination and typographic details.

Author(s): Hu, Nijia; Tanel, Meghan; Baker, Stuart N.; Kidgell, Dawson J.; Walker, Simon

Title: Inducing ipsilateral motor-evoked potentials in the biceps brachii muscle in healthy humans

Year: 2024

Version: Published version

Copyright: © 2024 The Author(s). European Journal of Neuroscience published by Federation

Rights: CC BY 4.0

Rights url: https://creativecommons.org/licenses/by/4.0/

Please cite the original version:

Hu, N., Tanel, M., Baker, S. N., Kidgell, D. J., & Walker, S. (2024). Inducing ipsilateral motor-evoked potentials in the biceps brachii muscle in healthy humans. European Journal of Neuroscience, Early View. https://doi.org/10.1111/ejn.16548

Check for updates

Received: 14 March 2024 | Revised: 4 September 2024 | Accepted: 9 September 2024

DOI: 10.1111/ejn.16548

SHORT COMMUNICATION

EJN European Journal of Neuroscience FENS WILEY

Inducing ipsilateral motor-evoked potentials in the biceps brachii muscle in healthy humans

Nijia Hu[1] | Meghan Tanel[1] | Stuart N. Baker[2] | Dawson J. Kidgell[3] | Simon Walker[1]

[1]NeuroMuscular Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

[2]Medical School, Newcastle University, Newcastle upon Tyne, UK

[3]Monash Exercise Neuroplasticity Research Unit, School of Primary and Allied Health Care, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia

Correspondence
Nijia Hu and Simon Walker, NeuroMuscular Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland.
Email: hunijia@gmail.com and simon.walker@jyu.fi

Funding information
SW received financial supported from The Research Council of Finland #350528.

Abstract

To assess reticulospinal tract excitability, high-intensity transcranial magnetic stimulation (TMS) has been used to elicit ipsilateral motor-evoked potentials (iMEPs). However, there is no consensus on robust and valid methods for use in human studies. The present study proposes a standardized method for eliciting and analysing iMEPs in the biceps brachii. Twenty-four healthy young adults participated in this study. Electromyography (EMG) electrodes recorded contralateral MEPs (cMEPs) from the right and iMEPs from the left biceps brachii. A dynamic preacher curl task was used with ∼15% of the subject's one-repetition maximum load. The protocol included maximal compound action potential (M-max) determination of the right biceps brachii muscle, TMS hotspot determination, and four sets of five repetitions where 100% stimulator output was delivered at an elbow angle of 110° of flexion. We normalized cMEP amplitude by M-max (% M-max) and iMEP by cMEP amplitude ratio (ICAR). Clear iMEPs above background EMG were observed in 21 subjects (88%, ICAR = .31 ± .19). Good-to-excellent agreement (intra-class correlation coefficient [ICC] = .795–1.000) and low bias (.01–.08 mV and .60–1.11 ms) were demonstrated when comparing two different analysis methods (i.e. fixed time-window vs. manual onset detection) to determine the cMEP and iMEP amplitude and latency, respectively. Most subjects demonstrated clear iMEPs above background EMG triggered at a pre-determined joint angle during a light-load dynamic preacher curl exercise. Similar results were obtained when comparing a single-trial manual identification of iMEP and a semi-automated time-window data analysis approach.

KEYWORDS
motor-evoked potential, preach curl, reticulospinal tract, strength training, transcranial magnetic stimulation

Abbreviations: CI, confidence interval; cMEP, contralateral motor-evoked potential; EMG, electromyography; ICC, intraclass correlation coefficient; ICAR, ipsilateral to contralateral amplitude ratio; iMEP, ipsilateral motor-evoked potential; M-max, Maximum M-wave; RMS, root mean square; TMS, transcranial magnetic stimulation.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
© 2024 The Author(s). *European Journal of Neuroscience* published by Federation of European Neuroscience Societies and John Wiley & Sons Ltd.

1 | INTRODUCTION

Voluntary contraction in humans is mainly controlled by the corticospinal tract which is the most important descending pathway from the motor cortex to the skeletal muscles (Fromm & Evarts, 1982). In the medulla oblongata, most fibres decussate to the opposite side (Marshall, 1936). Therefore, the motor cortex innervates voluntary activity of the contralateral limb's muscle in mammals. Transcranial magnetic stimulation (TMS) is a widely used non-invasive tool to evaluate corticospinal excitability in human research. A contralateral motor-evoked potential (cMEP) in the target muscle can be elicited and recorded by surface electromyography (EMG) (Hortobágyi et al., 2003). cMEP amplitude and latency have been used to quantify corticospinal excitability (Ziemann et al., 1999).

The reticulospinal tract originates in the brainstem's reticular formation (pons and medulla) and descends bilaterally parallel to the corticospinal tract along the spinal cord (Nathan et al., 1996). It is part of the extrapyramidal system and is a decisive subcortical structure involved in human locomotion and muscle tone (Grillner, 2011; Rothwell, 2012). The reticulospinal tract is involved in postural control, strength, motor recovery, and other gross motor functions (Baker, 2011; Baker & Perez, 2017; Glover & Baker, 2022). It has recently been hypothesised that the reticulospinal tract contributes to neural adaptation observed during resistance training in humans (Akalu et al., 2023; Atkinson et al., 2022; Glover & Baker, 2020). Therefore, it is crucial to develop suitable methodologies to evaluate reticulospinal functioning.

Motor-evoked potentials can be induced in the ipsilateral muscle by TMS under certain conditions, resulting in ipsilateral MEP (iMEP) recordings. It has been suggested that iMEPs fulfilling certain criteria could be used to assess reticulospinal function in humans (Maitland & Baker, 2021; Ziemann et al., 1999). Here, MEP latencies need to be considered. The high output from TMS may induce an 'iMEP' through current spreading to the opposite motor cortex, thus depolarizing pyramidal cells in both hemispheres simultaneously. In this situation, the 'iMEP' latency would be typically less than 4 ms longer than the cMEP latency (Ziemann et al., 1999). Thus, previous authors have suggested that a latency longer by 5–13 ms provides confidence of subcortical origin (Maitland & Baker, 2021; Ziemann et al., 1999).

Human studies have utilized iMEPs, mainly in upper limb muscles to indicate reticulospinal excitability. However, most of these studies elicited iMEPs in isometric muscle contraction tasks with mixed results. One study (Tazoe & Perez, 2014) was able to induce valid iMEPs in only 65% of the recruited subjects (mean age 28). Thus, isometric contraction, where the limb position remains fixed, may not adequately engage the reticulospinal tract, particularly at low force levels, leading to a potential loss of subjects. The most convincing evidence of the potential to measure iMEPs consistently and robustly in humans was presented by Maitland and Baker (2021), who elicited valid iMEPs in 88% of the recruited subjects; only some were not possible to measure in those >55 years old. However, while this study used a dynamic rowing task with a resistance band, such a method does not allow quantification and consistency of the resistance prior to TMS nor does it allow consideration of the maximal strength of the subject (i.e. testing at the same absolute force level vs. the same relative force level). Therefore, the purpose of this study was to present a standardized method to robustly elicit and analyse iMEPs in the biceps brachii of healthy adults.

2 | MATERIALS AND METHODS

2.1 | Subjects and study design

Subjects were obtained by convenience sample of university students and staff. Subjects were considered healthy, free from neurological and musculoskeletal diseases, not taking medication that could interfere with the study results and they did not present any contraindications for TMS measurements (Rossi et al., 2011). All subjects were considered right-arm dominant according to their response to the question "which arm do you prefer to throw a ball with?". The study was conducted according to the Declaration of Helsinki, except for pre-registration in a database.

Twenty-four subjects (12 males and 12 females, age: 31 ± 6 years, height: 173 ± 7 cm, body mass: 74 ± 14 kg) volunteered. Among the subjects, seven males and five females performed regular strength training defined as participating in gym sessions at least once per week in the past year. Each subject participated in one test session, which included the estimation of one-repetition maximum (1RM) preacher curl (i.e. bilateral elbow flexion exercise), maximal compound action potential (M-max) determination of the biceps brachii muscle, TMS hotspot determination, and four sets of five repetitions with ∼15% of 1RM where TMS was delivered at an elbow angle of 110° of flexion.

2.2 | Electromyography recording and analysis procedures

Bipolar surface Ag/AgCl electrodes (22 × 44 mm, Ambu BlueSensor N, Ballerup, Denmark) were placed according to SENIAM guidelines (Hermens et al., 1999) on the belly of the biceps brachii of both the right and left arms. The

14609568, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejn.16548 by University Of Jyvaskylä Library, Wiley Online Library on [09/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ground electrode was placed on the olecranon. Impedance was < 2 kΩ, the interelectrode distance was 20 mm, and the self-adhesive electrodes were further fixated using medical tape (Leukoplast, BSN medical Ltd, UK). EMG data were amplified (500 gain) and bandpass filtered (16–1000 Hz, NeuroLog system NL844, Digitimer Ltd, Welwyn Garden City, UK) prior to being sampled (3000 Hz) and converted via a 16-bit A/D board (Micro3-1401) to Spike2 software (version 6.10, Cambridge Electronic Design Ltd, Cambridge, UK).

2.3 | M-max procedures

Electrical stimulation (400 V compliance, 500 μs, square pulse) of the musculocutaneous nerve was delivered by a constant current stimulator (Model DS7AH, Digitimer Ltd, Welwyn Garden City, UK) to self-adhesive circular electrodes (30 mm diameter, PolarTrode, Niva Medical Ltd, Espoo, Finland) positioned with the cathode in Erb's point (supraclavicular fossa) and anode on the acromion process of the right arm targeting the right biceps brachii. An initial stimulation was delivered at 20 mA, and subsequent stimulations were delivered with increasing 10 mA steps until a plateau in EMG response was observed. Then, an additional 25% current intensity was used to stimulate the nerve in three, single pulses separated by 5–10 s. M-max was determined as the largest peak-to-peak amplitude (in mV) from one of the three confirmatory supra-maximal stimulations.

2.4 | TMS procedures

A figure-of-eight coil (70 cm winding diameter, D70 Alpha Flat Coated coil) and Magstim BiStim^2 magnetic stimulator (Magstim Co Ltd, Whitland, UK) were used to deliver monophasic current waveforms to the left motor cortex. The coil was placed tangential to the scalp and at 45° to the midsagittal plane, so that it induced a posterior–anterior current flow. The stimulation location was initiated 3 cm lateral from the vertex moving in ∼.5 cm steps until the largest cMEP response was produced using a stimulator output of 50%. Following minor anteroposterior adjustments (∼1–2 cm) to confirm the highest amplitude location, this was considered the hotspot. The hotspot was recorded by markings on the subject's scalp relative to the coil and held constant for each stimulation. The stimulator output was adjusted to 100% of the stimulator output at the cMEP hotspot to elicit iMEP for all stimulations. Although there is evidence that iMEPs may not be maximized at higher stimulation intensities (Ferbert et al., 1992; Wassermann et al., 1991), our pilot trials did not show differences in ipsilateral to contralateral amplitude ratio (ICAR) values when stimulating at 70%, 80%, 90% or 100% of stimulator output. We chose to use the BiStim^2 operated 100% by 'simultaneous mode' that both units discharge with 0 ms delay (Do et al., 2020). It provides ∼113% stimulator output compared to a single Magstim 200^2 unit (Magstim website: https://www.magstim.com/us-en/magstim-bistim2/), to ensure that cMEP amplitudes would be saturated.

2.5 | Preacher curl procedures

Subjects sat on a preacher curl bench (HUR Ltd, Kokkola, Finland) angled at 40° and rested their upper arms and chest on the support pads as depicted in Figure 1a. Using a supinated grip, the hands were shoulder-width apart and the minimum barbell mass was 8 kg (Leoko Ltd, Tampere, Finland). An electro-mechanical goniometer (University of Jyväskylä, Finland) was attached to the skin proximally and distally to the right elbow joint. The elbow angle was adjusted to 110° of flexion, and the accompanying signal was converted to a target line within Spike2 software that was displayed on a screen 1 m in front of the subject. The subject was instructed to flex and extend the elbows in 5 s per repetition to keep a slow and controlled tempo. Once the target line was reached during the concentric action, TMS was triggered. Practice trials with only the barbell were allowed so that the subjects could learn the desired lifting tempo. Subjects performed four sets of five repetitions interspersed with a 2-min break between sets; thus, 20 stimulations were delivered in total. The load during the test represented 15% of the 1RM with a minimum load adjustment of 2.5 kg. None of the subjects reported fatigue or difficulties in performing the five repetitions within each set nor the entire 20 repetitions.

2.6 | Data process and statistical analyses

Two methods processed the average iMEP value (i.e. peak-to-peak amplitude and latency). In the first method (Meth_ind), we assessed iMEP latency trial-by-trial by determining the presence of a distinct iMEP over a 200-ms window about the stimulation artifact. A clear iMEP was defined as a waveform with root mean square (RMS) amplitude at least 150% of the RMS amplitude of the background EMG (manually measured 100 ms before simulation) or a clear silent period (Wilson et al., 1993). If a clear iMEP was observed ('YES'), the iMEP from this trial was marked and collected for analysis; if not ('NO'), that trial's iMEP was excluded from

14609568, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejn.16548 by University Of Jyvaskyla Library, Wiley Online Library on [09/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

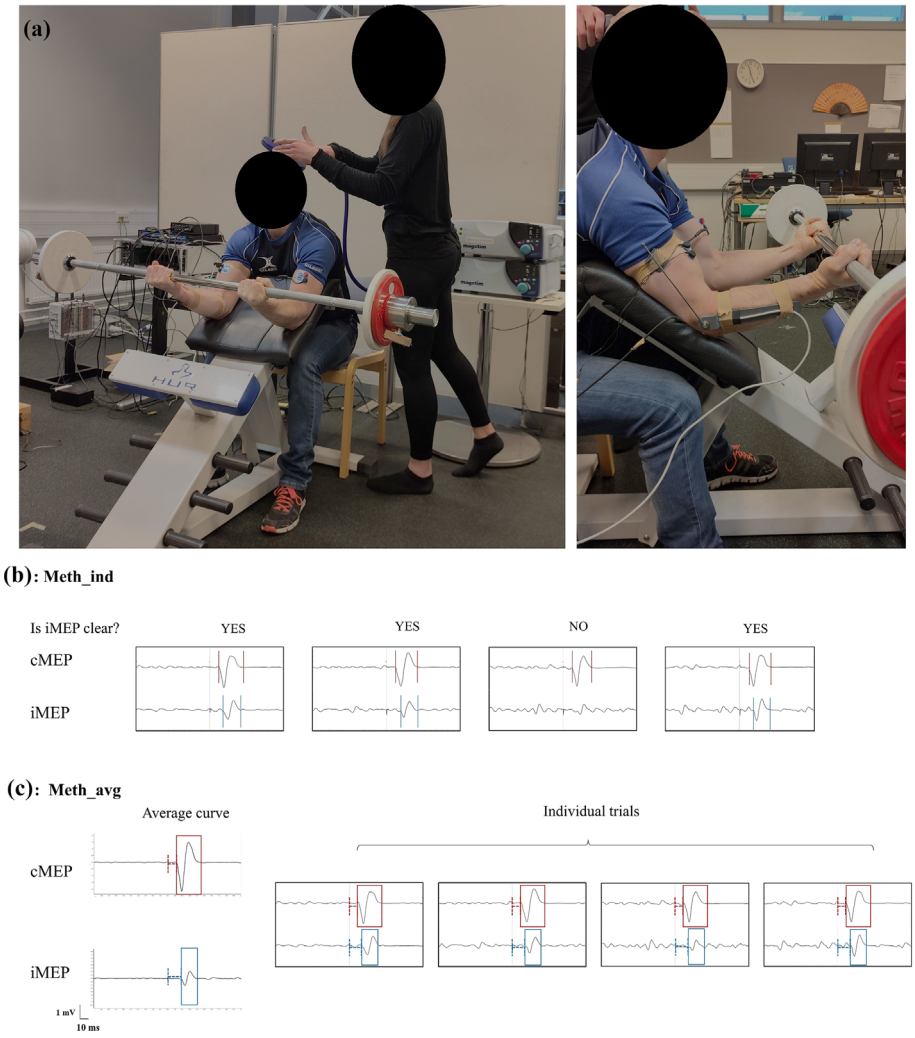

FIGURE 1 The measurement setup (a) shows the preacher curl bench, barbell, and EMG and TMS coil placements. The goniometer monitoring the elbow angle was fixed on the right arm. The screen displaying elbow angle and EMG traces to the subject for real-time feedback is not shown in the figure. Example trials from the same subject are shown in the figure by using Meth_ind (b) and Meth_avg (c) to analyse iMEP values. A 200-ms window around the stimulation artifact is shown in each cMEP/iMEP example.

subsequent calculations (Figure 1b). The putative iMEP was excluded if its latency was < 4 ms longer than the cMEP latency (Ziemann et al., 1999). Therefore, only clear iMEPs were included in the calculation of average values using Meth_ind. In another method (Meth_avg), an average iMEP curve was initially calculated, and a window spanning the iMEP onset to its end was established. By using the same window for all trials (Figure 1c), iMEPs from all stimulation trials were gathered for the final calculation of the average peak-to-peak value.

Statistical analyses were conducted using IBM SPSS 20.0 (SPSS, Chicago, USA). Results are displayed as mean ± standard deviation. cMEP was normalized by maximal M-wave (M-max). The iMEP/cMEP ratio (ICAR) was calculated, which has been used to evaluate iMEP amplitude in previous studies (Bawa et al., 2004; Maitland & Baker, 2021). Meth_ind was utilized initially to describe the occurrence of clear iMEPs. To be accepted to further analyses for Meth_ind, it was required to demonstrate clear iMEPs in at least 25% of all trials (i.e. ≥ 5 clear iMEPs from 20 trials).

To determine agreement between the Meth_ind and Meth_avg methods, a paired *t*-test was used to compare amplitude and latency of cMEP and iMEP. A two-way mixed effects model intraclass correlation coefficients (ICCs) and Bland–Altman analysis were used to access agreement (Lee et al., 1989). Between-method agreement based on ICCs and 95% CIs were categorized as poor (ICC < .5), moderate (.5 < ICC < .75), good (.75 < ICC < .9), or excellent (ICC > .9). Bias was determined as the mean difference between methods, and 95% limits of agreement was represented as mean difference ± 2.08 standard deviation of the bias (95% CIs of *t*-distribution, $N = 21$). Linear regression was used to test potential proportional bias between methods (Martínez et al., 1999). Alpha was set at 0.05.

3 | RESULTS

Table 1 presents the cMEP and iMEP amplitudes, ICAR, cMEP and iMEP latencies for both the 21 subjects with a

14609568, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejn.16548 by University Of Jyvaskylä Library, Wiley Online Library on [09/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

clear iMEP, and across 24 subjects, analysed using the Meth_avg method. Three subjects failed to exhibit iMEPs as per our criteria, resulting in subsequent analyses reporting on 21 subjects (comprising nine males and 12 females, representing 88% of the total recruits) using the Meth_ind method. Of these, 18 subjects demonstrated clear iMEP counts ranging from 70% to 95%, while the remaining three exhibited counts between 25% and 50%. Figure 2 displays the cMEP and iMEP amplitude–latency plots for each accepted stimulation from eight subjects, with subject averages depicted in Figure 3a.

Average normalized cMEP showed higher than 100% M-max (Figure 3b). ICAR values varied between individuals widely (from .10 to .78; Figure 3c). No differences were observed between strength trained versus untrained individuals for cMEP amplitude (trained: 149 ± 105% M-max, untrained: 82 ± 40% M-max; $t_{[19]} = 1.943$ $P = 0.067$) or ICAR (trained: .30 ± .19, untrained: .33 ± .20, $t_{[19]} = -.294$, $P = 0.772$).

From the 21 subjects demonstrating clear iMEPs above 150% background EMG and/or a silent period, agreement between the Meth_ind and Meth_avg analysis methods showed no difference for cMEP amplitude (Meth_ind: 117 ± 84% M-max, Meth_avg: 116 ± 83% M-max, $t_{[20]} = 1.173$, $P = 0.255$; Figure 3b). Both methods demonstrated good-to-excellent ICC, and no potential proportional bias was observed between the methods (Table 2). However, ICAR was significantly lower with Meth_avg (.29 ± .19) compared to Meth_ind (.31 ± .19, $t_{[20]} = 3.228$, $P = 0.004$; Figure 3c).

TABLE 1 cMEP amplitude, iMEP amplitude, ICAR and latency of cMEP and iMEP from 21 (i.e. those accepted to Meth_ind) and all 24 subjects using the Meth_avg analysis method (mean ± standard deviation).

	21 subjects	24 subjects
cMEP (mV)	4.09 ± 1.89	3.88 ± 1.90
cMEP (% M-max)	116 ± 83	108 ± 81
iMEP (mV)	1.16 ± 1.15	1.14 ± 1.09
ICAR	.29 ± .19	.27 ± .19
cMEP latency (ms)	10.35 ± .80	10.85 ± 1.00
iMEP latency (ms)	16.90 ± 1.54	17.19 ± 2.18

Abbreviations: cMEP, contralateral motor-evoked potential; ICAR, iMEP/cMEP amplitude ratio; iMEP, ipsilateral motor-evoked potential.

4 | DISCUSSION

This study successfully detected iMEPs in 21 out of 24 subjects in biceps brachii during a dynamic task. Good agreement was demonstrated when using two different analysis methods to determine cMEP and iMEP amplitude and latency, suggesting that both methods are usable for these purposes.

4.1 | Measurement setup

In our study, clear iMEPs were not shown by three out of the 24 subjects. This proportion aligns with the findings of a previous study that employed a dynamic task

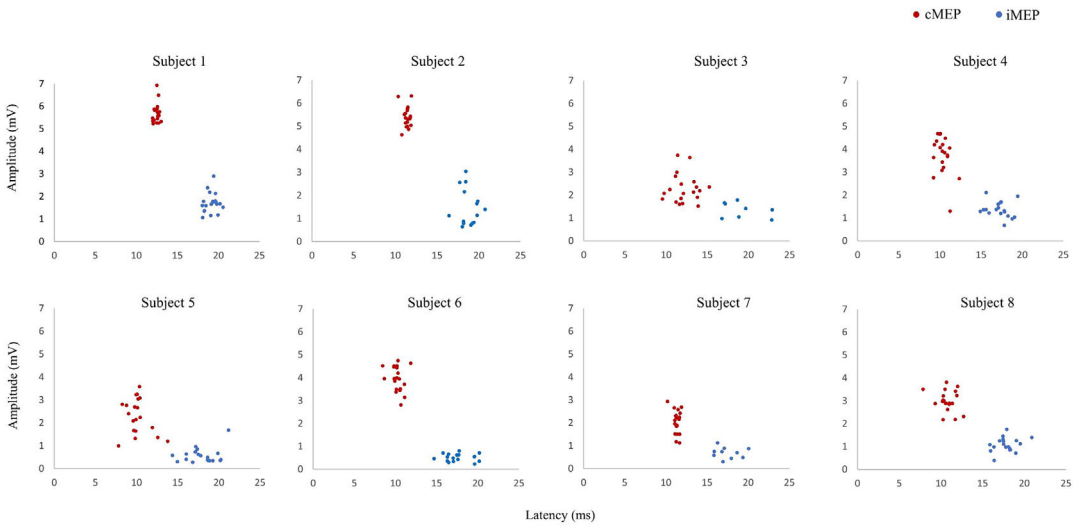

FIGURE 2 cMEP and iMEP amplitude–latency scatter plots showing single trials from eight example subjects. Red dots represent cMEPs (20 trials per subject), and blue dots represent observed and accepted iMEPs (trials vary between 8 and 20 per subject). Plots from all 24 subjects can be observed in an open database (10.6084/m9.figshare.26349526.v1).

14609568, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejn.16548 by University Of Jyvaskylla Library, Wiley Online Library on [09/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

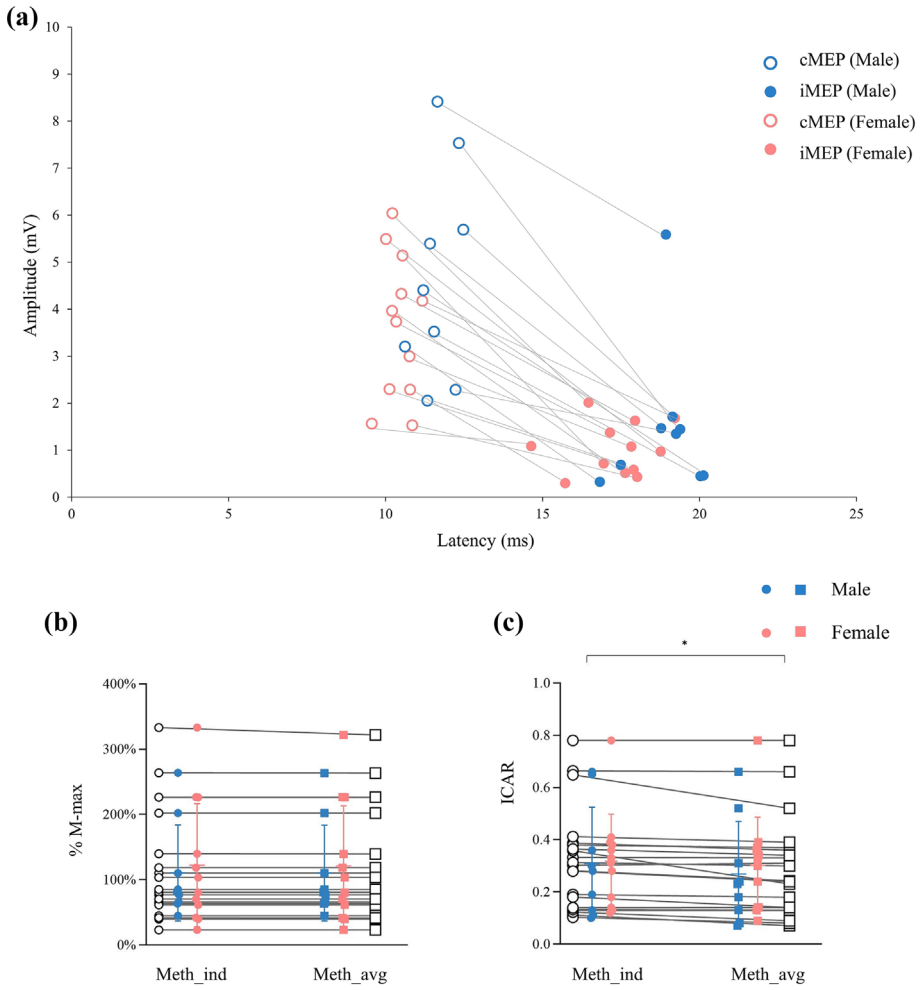

FIGURE 3 Scatter plot of cMEP and iMEP amplitude–latency with the mean of each subject (20 subjects in total) and the lines joining cMEP to iMEP identify each subject (a). cMEP (b) and ICAR (c) are shown by group average bar and standard deviation, along with individual results (red dots represent female subjects, $n = 12$; blue dots represent male subjects, $n = 9$).

TABLE 2 Between methods intraclass correlation coefficients (ICCs) and 95% coefficient intervals (CI) for Meth_ind and Meth_avg. Potential proportional bias between methods in each condition was compared by linear regression (*P*-value).

			Limits of agreement		
	ICC [95% CI]	**Bias**	**Lower**	**Upper**	***P*-value**
cMEP amplitude	1.000 [1.000, 1.000]	.01 (mV)	1.78 (mV)	1.90 (mV)	0.737
cMEP latency	.815 [−.161, .952]	.60 (ms)	−.04 (ms)	1.55 (ms)	0.989
iMEP amplitude	.997 [.986, .999]	.08 (mV)	.92 (mV)	1.31 (mV)	0.319
iMEP latency	.795 [−.129, .943]	1.11 (ms)	−.31 (ms)	3.07 (ms)	0.446
ICAR	.985 [.939, .995]	.03	.11	.26	0.824

Abbreviations: cMEP, contralateral motor-evoked potential; ICAR, iMEP/cMEP amplitude ratio; iMEP, ipsilateral motor-evoked potential.

(Maitland & Baker, 2021), and it is higher than what has been observed from isometric tasks (e.g. Tazoe & Perez, 2014). Altermatt et al. (2023) identified the iMEP hotspot within a radial distance of 1 cm from the cMEP hotspot. In their study, the same hotspot for cMEPs and iMEPs was found in nine out of 16 subjects, while the remaining seven subjects had different hotspots for cMEPs and iMEPs. Therefore, a potential methodological improvement could be to use individual hotspots for both cMEPs and iMEPs.

Previous studies have suggested that changes in elbow joint angle can influence corticospinal excitability via spinal level modulation, possibly due to multiple reflex inputs to the motoneuron pool (Forman et al., 2019; Nuzzo et al., 2016). Thus, both cMEP and iMEP amplitude could be affected by joint angle. To ensure the

14609568, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejn.16548 by University Of Jyvaskyla Library, Wiley Online Library on [09/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

stability of both arms during dynamic movements, subjects placed both arms and chest on the support pads. In addition, we consistently tracked the elbow angle during tempo lifting to elicit stimulations at precisely 110° elbow angle, which is proposed as the optimal length of biceps brachii muscle (Chang et al., 1999) to minimize reflex inputs and, thus, reduce variability.

High force contraction has been suggested to elicit iMEPs in healthy subjects and iMEP amplitude significantly increases with enhanced muscle contraction (Ziemann et al., 1999). This agrees with a reported monotonic increase of activation in the reticular formation with increasing contraction strength (Glover & Baker, 2022). ICAR of .12–.13 in biceps brachii has been previously demonstrated when using 100% TMS stimulation with 10% maximum voluntary contraction (Bawa et al., 2004). In the present study, muscle contraction was performed with 15% of 1RM load, and a higher average ICAR (.31) was demonstrated in our results compared to Bawa et al. (2004). Recently (Maitland & Baker, 2021), ICAR results in biceps brachii also demonstrated higher average values but large inter-individual variability (.02–.43), which was comparable with our results. This supports the proposal that higher iMEP amplitudes may be observed in dynamic and bilateral coordination muscle tasks (Altermatt et al., 2023). On the other hand, an unexpected negative correlation between ICAR and strength was observed (Maitland & Baker, 2021), potentially because the constant 12 kg load might not provide enough resistance to induce the required high-force contraction in subjects with greater strength.

One-hundred percent of stimulator output was used to elicit iMEPs in the present study, as used earlier (Tazoe & Perez, 2014; Wassermann et al., 1994). The current spread from the cMEP hotspot may excite neurons in the primary motor cortex or even other neurons that may influence iMEP generation (so-called corticoreticular projections). However, the source of the iMEPs is still unclear. Lower intensity (i.e. 80% of the stimulator output with Magstim 200) has successfully elicited iMEPs in biceps brachii (Bawa et al., 2004). Maitland and Baker's study (2021) used ∼65% stimulator output with Magstim 200^2 to prevent coil overheating during the experiment, which was not a concern in the present study since only 20 stimulations were given. By reducing the number of trials, researchers can reduce the risk of coil overheating and neuromuscular fatigue. While Ferbert et al. (1992) demonstrated that higher TMS intensity may induce interhemispheric inhibition, which could lead to suppression of corticospinal tract input to the motoneuron pool and reduced motoneuron excitability, we did not observe such a phenomenon during our pilot tests. Nevertheless, we cannot fully discount that 100% of simulator output is not optimal to induce the highest iMEPs on an individual level.

Overall, muscle contraction level affects iMEP accessibility, in which not only higher muscle activity leads to increased iMEPs in healthy adults, but also higher background EMG could mask low amplitude iMEPs in some individuals (Alagona et al., 2001; Guggenberger et al., 2022). The interplay between contraction intensity, stimulator output intensity, and the number of trials/contractions has not been fully resolved in this study. Regarding the number of trials, Ammann et al. (2020) showed that identifying the minimum number of trials is a futile exercise and increasing the number of trials beyond 10 has limited impact on MEP amplitude error. On the other hand, increasing the number of subjects has a greater effect and is advised (Ammann et al., 2020). Subsequent studies may, thus, aim to identify the optimal load and stimulator output for eliciting maximal iMEPs in a population-specific manner.

4.2 | iMEP analysis methods

It is important to note that there is no gold standard regarding iMEP detection. Even visual inspection is challenging because of the relatively high background EMG activity. We evaluated two methods used previously (McDonnell et al., 2004). Results show that iMEP amplitude/ICAR was significantly higher when using Meth_ind compared to Meth_avg due to removing low amplitude trials. Only clearly visible iMEPs were selected to calculate the final average iMEP with Meth_ind, whereas all trials were included and assessed according to a predetermined time window for Meth_avg. On the other hand, between-method ICC demonstrated good-to-excellent agreement and no potential proportional bias. This shows that differences between methods were consistent and, although one produces lower amplitudes, it should not adversely affect outcomes/interpretations in many experimental settings.

The precise source of the iMEPs is not well known, but they may be traced back to the cortical motor area, where signals travel via the corticoreticular tract eliciting potentials in the ipsilateral pontomedullary reticular formation then descend via the reticulospinal tract and finally elicit an iMEP in the target muscle (Fisher et al., 2012). It has been shown in non-human primates that this is the most common ipsilateral circuit when stimulated at the cortical motor area (Ortiz-Rosario et al., 2014). However, the synaptic connections involved in iMEP generation are not strictly in the ipsilateral side. The contralateral corticoreticular tract and pontomedullary reticular formation may transfer across and engage

14609568, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejn.16548 by University Of Jyvaskyla Library, Wiley Online Library on [09/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

with the ipsilateral reticulospinal tract, which may explain variations in iMEP latency observed between subjects and different studies.

Some limitations should be acknowledged. We followed previous methodology (Akalu et al., 2023; Maitland & Baker, 2021) in calculating ICAR from absolute EMG amplitudes in both arms. However, this assumes that the two signals propagate equally. This may lead to some unquantified error, and it may be more prudent to normalize both signals to M-max prior to calculating their ratio. Second, the sub-group sample size was relatively small and, although some comparisons between training status were made in the present study, we may have been underpowered. Therefore, it is still unclear whether utilizing iMEPs to determine training adaptation contains sufficient measurement sensitivity. Thus, future studies should determine the test–retest reliability of this method prior to implementing it, for example, when examining the effect of an intervention.

5 | CONCLUSION

In this study, a dynamic biceps brachii contraction with ~15% 1RM load and 100% stimulator output elicited iMEPs robustly in 21/24 healthy young adults. High level of agreement and strong associations suggests that either of the proposed analysis methods could be used for peak-to-peak iMEP amplitude/ICAR determination. No differences were observed in trained vs. untrained sub-groups, probably due to high inter-individual variability.

AUTHOR CONTRIBUTIONS

Nijia Hu: Data curation; formal analysis; methodology; writing—original draft. **Meghan Tanel:** Formal analysis; methodology; project administration. **Stuart N. Baker:** Formal analysis; methodology. **Dawson J. Kidgell:** Data curation; formal analysis; methodology. **Simon Walker:** Data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; supervision; writing—original draft.

ACKNOWLEDGEMENTS

Simon Walker received financial supported from The Research Council of Finland #350528.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16548.

DATA AVAILABILITY STATEMENT

Data for the experiments reported here can be made available upon reasonable request. Amplitude–latency plots for all 24 subjects are provided in an open database (10.6084/m9.figshare.26349526.v1).

ORCID

Nijia Hu https://orcid.org/0000-0001-5471-7873
Meghan Tanel https://orcid.org/0009-0009-7106-7118
Dawson J. Kidgell https://orcid.org/0000-0002-1800-382X
Simon Walker https://orcid.org/0000-0002-6804-0741

REFERENCES

Akalu, Y., Frazer, A. K., Howatson, G., Pearce, A. J., Siddique, U., Rostami, M., Tallent, J., & Kidgell, D. J. (2023). Identifying the role of the reticulospinal tract for strength and motor recovery: A scoping review of nonhuman and human studies. *Physiological Reports*, *11*(14), e15765. https://doi.org/10.14814/phy2.15765

Alagona, G., Delvaux, V., Gérard, P., De Pasqua, V., Pennisi, G., Delwaide, P. J., Nicoletti, F., & Maertens de Noordhout, A. (2001). Ipsilateral motor responses to focal transcranial magnetic stimulation in healthy subjects and acute-stroke patients. *Stroke*, *32*(6), 1304–1309. https://doi.org/10.1161/01.STR.32.6.1304

Altermatt, M., Jordan, H., Ho, K., & Byblow, W. D. (2023). Modulation of ipsilateral motor evoked potentials during bimanual coordination tasks. *Frontiers in Human Neuroscience*, *17*, 1219112. https://doi.org/10.3389/fnhum.2023.1219112

Ammann, C., Guida, P., Caballero-Insaurriaga, J., Pineda-Pardo, J. A., Oliviero, A., & Foffani, G. (2020). A framework to assess the impact of number of trials on the amplitude of motor evoked potentials. *Scientific Reports*, *10*, 21422. https://doi.org/10.1038/s41598-020-77383-6

Atkinson, E., Škarabot, J., Ansdell, P., Goodall, S., Howatson, G., & Thomas, K. (2022). Does the reticulospinal tract mediate adaptation to resistance training in humans? *Journal of Applied Physiology*, *133*(3), 689–696. https://doi.org/10.1152/japplphysiol.00264.2021

Baker, S. N. (2011). The primate reticulospinal tract, hand function and functional recovery. *The Journal of Physiology*, *589*(23), 5603–5612. https://doi.org/10.1113/jphysiol.2011.215160

Baker, S. N., & Perez, M. A. (2017). Reticulospinal contributions to gross hand function after human spinal cord injury. *Journal of Neuroscience*, *37*(40), 9778–9784. https://doi.org/10.1523/JNEUROSCI.3368-16.2017

Bawa, P., Hamm, J. D., Dhillon, P., & Gross, P. A. (2004). Bilateral responses of upper limb muscles to transcranial magnetic stimulation in human subjects. *Experimental Brain Research*, *158*(3), 385–390. https://doi.org/10.1007/s00221-004-2031-x

Chang, Y. W., Su, F. C., Wu, H. W., & An, K. N. (1999). Optimum length of muscle contraction. *Clinical Biomechanics (Bristol, Avon)*, *14*(8), 537–542. https://doi.org/10.1016/s0268-0033(99)00014-5

Do, M., Clark, G. M., Fuelscher, I., Kirkovski, M., Cerins, A., Corp, D. T., Bereznicki, H. G. K., Albein-Urios, N., & Enticott, P. G. (2020). Magstim 2002 and Bistim Mode

14609568, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejn.16548 by University Of Jyvaskyla Library, Wiley Online Library on [09/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

maximum stimulus output values are not equivalent: Configuration selection is critical. *Brain Stimulation*, *13*(2), 444–446. https://doi.org/10.1016/j.brs.2019.12.009

Ferbert, A., Priori, A., Rothwell, J. C., Day, B. L., Colebatch, J. G., & Marsden, C. D. (1992). Interhemispheric inhibition of the human motor cortex. *The Journal of Physiology*, *453*, 525–546. https://doi.org/10.1113/jphysiol.1992.sp019243

Fisher, K. M., Zaaimi, B., & Baker, S. N. (2012). Reticular formation responses to magnetic brain stimulation of primary motor cortex. *The Journal of Physiology*, *590*(16), 4045–4060. https://doi.org/10.1113/jphysiol.2011.226209

Forman, D. A., Abdel-Malek, D., Bunce, C. M. F., & Holmes, M. W. R. (2019). Muscle length and joint angle influence spinal but not corticospinal excitability to the biceps brachii across forearm postures. *Journal of Neurophysiology*, *122*(1), 413–423. https://doi.org/10.1152/jn.00620.2018

Fromm, C., & Evarts, E. V. (1982). Pyramidal tract neurons in somatosensory cortex: Central and peripheral inputs during voluntary movement. *Brain Research*, *238*(1), 186–191. https://doi.org/10.1016/0006-8993(82)90781-8

Glover, I. S., & Baker, S. N. (2020). Cortical, corticospinal, and reticulospinal contributions to strength training. *Journal of Neuroscience*, *40*(30), 5820–5832. https://doi.org/10.1523/JNEUROSCI.1923-19.2020

Glover, I. S., & Baker, S. N. (2022). Both corticospinal and reticulospinal tracts control force of contraction. *The Journal of Neuroscience*, *42*(15), 3150–3164. https://doi.org/10.1523/JNEUROSCI.0627-21.2022

Grillner, S. (2011). Neuroscience. Human locomotor circuits conform. *Science (New York, N.Y.)*, *334*(6058), 912–913. https://doi.org/10.1126/science.1214778

Guggenberger, R., Trunk, B., Canbolat, S., Ziegler, L., & Gharabaghi, A. (2022). Evaluation of signal analysis algorithms for ipsilateral motor-evoked potentials induced by transcranial magnetic stimulation. *Journal of Neural Engineering*, *19*, 036032. https://doi.org/10.1088/1741-2552/ac6dc4

Hermens, H. J., Freriks, B., Merletti, R., Stegeman, D., Blok, J., Rau, G., Disselhorst-Klug, C., & Hägg, G. (1999). European recommendations for surface electromyography. *Roessingh Research and Development*, *8*(2), 13–54.

Hortobágyi, T., Taylor, J. L., Petersen, N. T., Russell, G., & Gandevia, S. C. (2003). Changes in segmental and motor cortical output with contralateral muscle contractions and altered sensory inputs in humans. *Journal of Neurophysiology*, *90*(4), 2451–2459. https://doi.org/10.1152/jn.01001.2002

Lee, J., Koh, D., & Ong, C. N. (1989). Statistical evaluation of agreement between two methods for measuring a quantitative variable. *Computers in Biology and Medicine*, *19*(1), 61–70. https://doi.org/10.1016/0010-4825(89)90036-X

Maitland, S., & Baker, S. N. (2021). Ipsilateral motor evoked potentials as a measure of the reticulospinal tract in age-related strength changes. *Frontiers in Aging Neuroscience*, *13*, 612352. https://doi.org/10.3389/fnagi.2021.612352

Marshall, C. (1936). The functions of the pyramidal tracts. *The Quarterly Review of Biology*, *11*(1), 35–56. https://doi.org/10.1086/394499

Martínez, À., del Río, F. J., Riu, J., & Rius, F. X. (1999). Detecting proportional and constant bias in method comparison studies by using linear regression with errors in both axes. *Chemometrics and Intelligent Laboratory Systems*, *49*(2), 179–193. https://doi.org/10.1016/S0169-7439(99)00036-2

McDonnell, M. N., Ridding, M. C., & Miles, T. S. (2004). Do alternate methods of analysing motor evoked potentials give comparable results? *Journal of Neuroscience Methods*, *136*(1), 63–67. https://doi.org/10.1016/j.jneumeth.2003.12.020

Nathan, P. W., Smith, M., & Deacon, P. (1996). Vestibulospinal, reticulospinal and descending propriospinal nerve fibres in man. *Brain*, *119*(6), 1809–1833. https://doi.org/10.1093/brain/119.6.1809

Nuzzo, J. L., Trajano, G. S., Barry, B. K., Gandevia, S. C., & Taylor, J. L. (2016). Arm posture-dependent changes in corticospinal excitability are largely spinal in origin. *Journal of Neurophysiology*, *115*(4), 2076–2082. https://doi.org/10.1152/jn.00885.2015

Ortiz-Rosario, A., Berrios-Torres, I., Adeli, H., & Buford, J. A. (2014). Combined corticospinal and reticulospinal effects on upper limb muscles. *Neuroscience Letters*, *561*, 30–34. https://doi.org/10.1016/j.neulet.2013.12.043

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2011). Screening questionnaire before TMS: An update. *Clinical Neurophysiology*, *122*(8), 1686–1686. https://doi.org/10.1016/j.clinph.2010.12.037

Rothwell, J. C. (2012). *Control of human voluntary movement*. Springer Science & Business Media.

Tazoe, T., & Perez, M. A. (2014). Selective activation of ipsilateral motor pathways in intact humans. *Journal of Neuroscience*, *34*(42), 13924–13934. https://doi.org/10.1523/JNEUROSCI.1648-14.2014

Wassermann, E. M., Fuhr, P., Cohen, L. G., & Hallett, M. (1991). Effects of transcranial magnetic stimulation on ipsilateral muscles. *Neurology*, *41*(11), 1795. https://doi.org/10.1212/WNL.41.11.1795

Wassermann, E. M., Pascual-Leone, A., & Hallett, M. (1994). Cortical motor representation of the ipsilateral hand and arm. *Experimental Brain Research*, *100*(1), 121–132. https://doi.org/10.1007/BF00227284

Wilson, S. A., Lockwood, R. J., Thickbroom, G. W., & Mastaglia, F. L. (1993). The muscle silent period following transcranial magnetic cortical stimulation. *Journal of the Neurological Sciences*, *114*(2), 216–222. https://doi.org/10.1016/0022-510x(93)90301-e

Ziemann, U., Ishii, K., Borgheresi, A., Yaseen, Z., Battaglia, F., Hallett, M., Cincotta, M., & Wassermann, E. M. (1999). Dissociation of the pathways mediating ipsilateral and contralateral motor-evoked potentials in human hand and arm muscles. *The Journal of Physiology*, *518*(3), 895–906. https://doi.org/10.1111/j.1469-7793.1999.0895p.x

How to cite this article: Hu, N., Tanel, M., Baker, S. N., Kidgell, D. J., & Walker, S. (2024). Inducing ipsilateral motor-evoked potentials in the biceps brachii muscle in healthy humans. *European Journal of Neuroscience*, 1–9. https://doi.org/10.1111/ejn.16548

14609568, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ejn.16548 by University Of Jyvaskyla Library, Wiley Online Library on [09/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License