

Nociceptive influence on cortical output within proximal-distal muscles in the upper-limb.

Running title: Nociceptive influence on cortical output of upper-limb muscles.

Nathanial R. Eckert¹, Davin Greenwell², Brach Poston³, Zachary A. Riley²

¹*Department of Kinesiology, University of Indianapolis – Indianapolis Center for Exercise Research [ICER], Indianapolis, IN, 46227 USA*

²*Department of Kinesiology, Indiana University-Purdue University, Indianapolis, IN, 46202 USA*

³*Department of Kinesiology and Nutritional Sciences, University of Nevada-Las Vegas, NV, USA*

Corresponding Author:

Nathanial R. Eckert

Email: eckertnr@uindy.edu

ORCID: 0000-0002-0236-1809

Telephone: (812) 788-8530 USA

University of Indianapolis, College of Health Sciences, Department of Kinesiology
1643 E. Hanna Ave.

Indianapolis IN 46227

Competing Interests: None of the listed authors have any conflicts of interest.

Data Availability Statement: The raw data associated with the collection and analysis presented within the following manuscript are not publicly available. This is due to the age of the data surpassing 7 years requiring data deletion per IRB regulations.

Funding: No funding was acquired for the work presented in the following manuscript.

Abstract

A single pulse of high intensity electrical current delivered to the digits of the hand during voluntary contractions produces a period of decreased electromyographic (EMG) activity, known as a cutaneous silent period (CSP) (Caccia G and Violini A, 1973;Inghilleri M et al., 1997;Uncini A et al., 1991). Pairing transcranial magnetic stimulation (TMS) with digit stimulation results in motor evoked potentials (MEPs) with reduced amplitudes in a thenar muscle (Kofler, 2008). It is not known if similar behavior can be observed in more proximal upper-limb muscles. The current study investigated the CSP on several muscles throughout the upper-limb. 14 subjects performed isometric contractions with the following muscles: abductor pollicis brevis (APB), flexor carpi radialis (FCR), extensor carpi radialis (ECR), biceps brachii (BIC), triceps brachii (TRI), anterior deltoid (AD), and posterior deltoid (PD). During the isometric contractions, subjects experienced three different stimulation conditions: electrical stimulation (10x perceptual threshold) of digit II only (CSP), transcranial magnetic stimulation only (TMS), and a pairing of digit II stimulation and TMS (TMS+). The TMS evoked MEP was significantly greater than the TMS+ MEP for APB ($p < 0.001$), FCR ($p = 0.006$), and BIC ($p < 0.049$) muscles. The opposite relationship was seen within the PD ($p < 0.047$) muscle. An ANOVA test of normalized MEP values (TMS+/TMS) showed significant differences in APB vs TRI ($p = 0.004$) and PD ($p = 0.003$), and in FCR vs TRI ($p = 0.046$) and PD ($p = 0.037$) muscles. The results suggest that the CSP modulates descending drive differentially across upper-limb muscles.

Keywords: Cutaneous Silent Period, Motor Control, Spinal Reflex

Introduction

Human movement is a complex process that requires the integration of descending motor commands with ascending sensory information to inform and shape a desired movement. This interaction is clearly observed when moving through an environment filled with unpredictable objects or interactions as our movement becomes more responsive to sensory feedback from areas such as the fingertips (Wolpert DM and Flanagan JR, 2001). It becomes reasonable then, to investigate what happens when sensory feedback from an outside force, such as a high-intensity stimulation event, interrupts a desired movement. During periods of motor inactivity high-intensity stimulation has been shown to reflexively excite motor neurons and produce motor output such as a flexion withdrawal reflex (Floeter MK et al., 1998). The opposite result can be seen within periods of motor activity in which the introduction of high-intensity stimulation can result in decreased muscle activity, known as a cutaneous silent period (CSP) (Kofler M, 2003;Kofler M et al., 2019). These nociceptive reflexes show just how easily sensory input can modify muscle activity even during periods of intentional, goal-directed movement (Serrao M et al., 2006). However, there is limited evidence on how these reflexes, when evoked with electrical stimulation, directly interact with descending motor commands to modify movement.

Pairing spinal reflexes with direct motor cortex stimulation provides the means to investigate complex interactions between supraspinal and spinal inputs capable of influencing the overall motor response to peripheral afferent input. For example, as generally discussed earlier, during voluntary contractions the introduction of high-intensity electrical stimulation to the digits of the hand produces a brief period of decreased electromyographic activity (EMG), or CSP, within the muscles of the upper-limb (e.g. thenar, triceps brachii) (Caccia MR et al., 1973;Inghilleri M,Cruccu G,Argenta M,Polidori L and Manfredi M, 1997;Kofler M, 2004;Uncini A,Kujirai T,Gluck B and Pullman S, 1991). Pairing the CSP with transcranial magnetic stimulation (TMS) enables the study of the interaction between the inhibitory CSP reflex and the excitatory descending drive (motor-evoked potentials [MEP]) from the motor cortex. Previous work utilizing this technique has demonstrated that MEPs produced within the duration of the

CSP become suppressed rather than eliminated, especially within the muscles of the hand (Farina S et al., 2001;Inghilleri M,Cruccu G,Argenta M,Polidori L and Manfredi M, 1997;Kofler M et al., 1998;Le Pera D et al., 2001). This provides direct evidence that the inhibitory spinal circuitry associated with peripheral noxious stimuli have the ability to modify the descending commands coming from higher brain centers. However, this evidence has been largely isolated to individual muscles of the hand and forearm, and therefore fails to provide a comprehensive view of how these interactions take place across the upper-limb.

As mentioned, previous studies have limited their investigations to examining the influence of the CSP on the descending input for distal muscles (i.e. hand and/or forearm) of the upper-limb. However, previous investigations have demonstrated that CSP duration decreases from distal to proximal muscles suggesting that the inhibition, arising from the post-synaptic input from A δ fibers, was stronger onto distal muscles motor neurons (Inghilleri M,Cruccu G,Argenta M,Polidori L and Manfredi M, 1997). The possibility exists that influence of the CSP on descending input to more proximal muscles would exert different effects. Therefore, the purpose of the current study was to determine the influence of high-intensity electrical stimulation (e.g. CSP) on the excitatory descending drive to several distal-to-proximal muscles of the upper-limb. From a functional perspective, similar levels of inhibition on muscles throughout the upper limb, in response to painful stimuli, remains implausible; as protecting the upper-limb from further insult may require activation rather than inhibition, depending on the context. Therefore, it may be hypothesized that the level of MEP suppression would be significantly different when comparing distal and proximal muscles. The results presented may help determine the spinal organization of small-diameter afferent input within the muscles of the upper-limb, allowing for a more comprehensive understanding of how sensory, in this case nociceptive input, is processed in reference to upper-limb motor control.

Experimental Procedures

Participants

14 healthy, university-aged adults (8 males/6 females; 23 ± 5 yrs) participated in the study. All subjects had previously had their CSPs tested previously where their reflex onset and offset times were recorded (Eckert NR et al., 2018). Subjects' self-reported no neurological disorders or other upper-limb musculoskeletal impairments. Each subject provided an informed consent prior to participating. The protocol was approved by the Indiana University Institutional Review Board and was performed in accordance with the Declaration of Helsinki.

Experimental Design

Apparatus and Testing Environment

All subjects were seated upright and provided visual feedback via a computer monitor placed at eye level in front of the subject (Fig 1A). The subject's right arm was placed (elbow flexion 90° ; shoulder $\sim 45^\circ$ abduction from torso), unrestricted, in a custom arm apparatus. The subjects were instructed to grasp an immovable handle attached to a tri-axial force transducer (JR3 Inc., CA, USA), fully grasped, thumb wrapped around, or through "cupping the hand" depending on the muscle action necessary (Fig 1A-C). Electrical stimulation was delivered to Digit II of the right hand with a Digitimer DS7AH constant current electrical stimulator (Digitimer LTD, England, UK) that sent the electrical current through ring electrodes. Motor evoked potentials (MEPs) were evoked with TMS (Magstim 200; Magstim LTD, UK) delivered through a D70 remote coil (double 70mm windings) to the left motor cortex. Electromyographic (EMG) activity was recorded from the abductor pollicis brevis (APB), flexor carpi radialis (FCR), extensor carpi radialis (ECR), biceps brachii long head (BIC), triceps brachii lateral head (TRI), anterior deltoid (AD), and posterior deltoid (PD) muscles of the right arm (Fig 1D). Each electrode was placed over the specific muscle belly, parallel to the orientation of the respective muscle's fibers with a common ground electrode placed over the spinous process C7 (Criswell E, 2010). EMG was sampled at 2,000 Hz using rectangular single differential bar electrodes on a 16-channel Bagnoli EMG system (Delsys Inc, MA, USA) with high- and low-pass cut-off frequencies of 20Hz and 500Hz, respectively. All data was stored at a final gain of 1,000x with Spike2 software (CED, Cambridge, UK).

Experimental Protocol

First, subjects were asked to perform three maximal voluntary contractions (MVCs) for each of the recorded muscles. Subjects were instructed to contract as hard as possible while maintaining an upright posture and arm position. Each MVC was produced isometrically against the vertical handle attached to the custom arm setup. The investigators monitored the subjects arm placement and associated EMG to ensure the isolated muscle contraction had minimal activation from the supporting musculature. If the subject had trouble isolating a given muscle contraction, as dictated by a large amount of synergistic muscle activation, the subject was asked to relax and try again. Of the three MVC's, the one with the highest peak value was used to determine 5% of the subject's MVC for that respective muscle. A horizontal line representing this 5% value was set on a monitor in front of the subject to serve as the visual feedback for the trials. In an effort to make this easier to follow, the EMG display was rectified and smoothed over a 100ms window set over the 5% EMG matching line, as performed in previous investigations (Eckert NR, Poston B and Riley ZA, 2018). During testing, subjects were instructed to match the 5% MVC line with their EMG activity for that specific muscle by contracting that specific muscle while holding the handle. Similar to the MVC testing, subjects were instructed to minimize activation of supporting musculature while investigators constantly monitored co-activation in the EMG. As the subject maintained this muscle contraction, they received 10 of each (30 total) of the following stimulation conditions at a randomly selected rate between 0.33-0.5Hz: Digit II stimulation only, TMS only, TMS+ Digit II stimulation (noted as Digit II, TMS, and TMS+, respectively, throughout the paper). Stimulations were delivered in a randomly selected order between conditions. Subjects completed a 2-3 minute rest period following each muscle trial and the order of muscles tested was randomized for each subject. At the conclusion of the testing the distance (cm) from the spinous process C7 to the EMG electrode placement for each muscle was taken. This measurement provided a general distance indicator for each electrode, representing the muscle location, from the spinous process C7 to allow for generally testing of any potential differences within reflex response as a measure of general distance from the spinal cord.

Stimulation Parameters

Testing of each muscle followed a distal to proximal progression starting with the APB muscle and ending with the PD muscle. In total, in this testing session, subjects received 70 TMS only, and 70 TMS+ stimulations across the entire upper-limb.

Digit II Stimulation

Noxious electrical stimulation (square-wave pulses, 0.5ms duration) was delivered to digit II of the right hand with a Digitimer DS7AH constant current electrical stimulator (Digitimer LTD, England, UK). Sensory or perceptual threshold was first determined by slowly increasing the electrical current until perceivable by the subject. Five stimuli were then randomly delivered and the subject had to detect all five to ensure the accuracy of the perceptual threshold. The level of stimulus intensity utilized during the experiment was set at 10x perceptual threshold. This resulted in a stimulus intensity typically between 30—50 mA for most subjects, which is consistent with other studies in the upper-limb (Kofler M, 2003).

TMS Stimulation

Single TMS stimuli were delivered using a standard Magstim 200² stimulator (Magstim Company LTD, UK) with a 70 mm figure-of-eight shaped coil. The coil handle was pointing 45° to the posterior and the figure-of-eight coil was situated tangential to the skull while the subject wore a tight-fitting nylon cap. Stimulation was then delivered over the left hemisphere, contralateral to the right associated muscle, depending on the muscle being tested (Fig 1A). With the subject relaxed, supra-threshold stimulation was used to determine the optimal position for stimulation of the specific muscle's cortical representation. After determining the optimal position, the resting motor threshold (RTh) was determined with step-wise increases in stimulator output. Threshold was determined when the MEP responses was clearly discernable in 5 out of 10 consecutive stimuli. The stimulation site was then marked on the cap. TMS intensity during the experimental protocol was then set at 120% RTh based on the response at the optimal stimulation site for each muscle.

TMS+ Stimulation

From previous data, the average CSP onset time for each muscle had been calculated across the subjects (Eckert NR, Poston B and Riley ZA, 2018). This allowed for the precise determination of stimulation timing to allow for the MEP to arrive within the CSP (Fig 2), which was visually confirmed for each subject during testing. Specifically, the TMS stimulation was preprogrammed to occur after Digit II stimulation at predetermined times (i.e. APB-52ms, FCR-60ms, ECR-60ms, BIC-70ms, TRI -70ms, AD-67ms, PD-67ms) based on the average CSP onset times plus the conduction velocity of the MEP as determined via previous studies (Švilpaukaitė J et al., 2006). The intensity of Digit II and TMS stimulation was an exact match as described above with the exception of the pairing of the stimulations.

Data Analysis

Each of the EMG signals were processed with the CSP and MEP responses identified visually by the investigator with the help of a custom-made program written in MATLAB (Mathworks, MA, USA) by first removing the DC offset and rectifying the EMG signals. The series of stimulations were averaged and superimposed to ensure reproducibility when identifying the phases of the reflex response (Fig 2). A custom algorithm was written within MATLAB to determine the average background EMG level from a 100ms pre-stimulus baseline period (-100ms—Stimulation), from which a superimposed horizontal line representing an 80% decrease of the mean EMG activity was placed to determine a suppression of EMG activity from baseline (Kofler M, 2003). The individual inhibitory period was identified within each reflex response (Garnett R and Stephens JA, 1980). The inhibitory period was identified as a drop in the baseline EMG activity (onset) and then an EMG rebound back above 80% (offset). This suppressed period of EMG was considered the inhibitory period as long as the duration of the suppressed EMG was greater than 5ms. The time points for the onsets and offsets for each phase of the reflex response were identified as the intersection of the superimposed horizontal line of the mean EMG activity recorded and then, from that, the duration of the inhibitory period was calculated. In addition, the % of inhibition was calculated by dividing the level of

EMG activity during the inhibitory phase by the baseline EMG amplitude calculated from the 100ms pre-stimulus window (Kofler M, 2003;Kofler M, 2004).

MEPs were visually identified from a section of the EMG trace for each muscle that ranged 300ms prior to the TMS stimulation to 300ms post TMS stimulation. The onset and offset of the MEP was collected from that EMG trace in which the peak-to-peak value was determined by taking the maximum and minimum values of that time frame. Normalized MEP values were then determined for each muscle and subject by taking the average conditioned MEP amplitude and dividing it by the unconditioned MEP amplitude.

Statistical Analysis

Statistical analyses were performed utilizing the statistics toolbox in MATLAB (Mathworks, MA, USA). Two-way ANOVAs were used to compare the onsets, offsets, duration of inhibition, suppression level of EMG, and normalized motor evoked potentials (MEPs) within each muscle as well as across the collapsed data for both stimulation and muscles. Post-Hoc tests utilizing the Sheffe model were conducted in order to determine the direction of any individual differences that occurred. T-test analysis was used to compare the MEPs for both the TMS and TMS+ conditions to determine any significant differences. Linear regressions were then used to determine any if any significant relationships occur between variables of the pre-collected CSP, and normalized MEP responses with that of the distance of the muscle from the spinal cord. All results were considered significant at $p < 0.05$.

Results

Motor Evoked Potential Suppression

The results of the experimental protocol demonstrated a clear suppression of MEPs within the more distal muscles of the upper-limb and a clear facilitation in the more proximal muscles of the upper-limb, when paired with the CSP response. This is best seen in an averaged (across 10 stimulations) representative trace (Fig 3) for the Digit II (for CSP reference), TMS, and TMS+ conditions for one distal (APB) and proximal

muscle (PD) from one subject. T-tests comparing the TMS and TMS+ conditions resulted in significantly different MEP amplitudes within specific muscles. The MEP amplitude was significantly higher ($p < 0.05$) for the TMS condition when compared to the TMS+ condition for the APB ($p = 0.001$), FCR ($p = 0.0055$), and BIC ($p = 0.049$) muscles (Fig 4). The results also suggest that the relationship between the TMS and TMS+ conditions may be reversed within the more proximal muscles of the shoulder (i.e AD and PD). However, the PD ($p = 0.047$) was the only shoulder muscle having a significantly higher TMS+ MEP amplitude response when compared to the TMS condition.

Spinal Reflex Organization

To investigate a potential relationship between the TMS and TMS+ conditions, MEPs were normalized and compared using a one-way ANOVA across muscles. After being normalized (TMS+ MEP/TMS MEP), MEP mean values resulted in a significant main effect ($F(1,13) = 10.795, p < 0.001, d = 1.24$, Fig 5). Specifically, the APB was significantly different when compared to the ECR ($p = 0.026$), TRI ($p = 0.048$), AD ($p = 0.011$), and PD ($p = 0.015$). Regression analysis demonstrated a significant relationship ($p < 0.001$) between the normalized MEP values and muscle distance, previously collected CSP reflex duration, and previously collected CSP reflex suppression level. Specifically, a moderate to strong relationship was found between the normalized MEP and muscle distance from the spinal cord ($F = 27.977$, adjusted $r^2 = -0.54$) and a weak relationship with CSP reflex duration ($F = 34.462$, adjusted $r^2 = -0.28$) and CSP reflex suppression level ($F = 30.669$, adjusted $r^2 = 0.26$) (Fig 6).

Discussion

The present study sought to investigate the potential influence that peripheral nociceptive input may have on excitatory descending drive from the motor cortex. The main findings suggest the potential for a differential level of control for the CSP across the upper-limb. MEP suppression was found to be greatest within the distal muscles, with the amount of suppression directly related to the distance of the recorded muscle from the spinal cord. Interestingly, the MEP was facilitated within the more proximal muscles, the inverse of what was displayed within the distal muscles. Taken together these results suggest that

nociceptive input may differentially influence the distal and proximal muscles in what can be hypothesized to be an attempt to provide optimal protection for the upper-limb.

The current literature associated with the CSP conceptually centers around idea that the CSP serves as a portion of a complex reflexive action by “turning off” muscle synergies (Leis A et al., 2000). This level of complexity is exemplified as CSPs are manifested through different inhibitory patterns (i.e. timing/magnitude of response) that are potentially paired with excitatory patterns which, together, allow for precise manipulation and exploration/control of the environment or specific objects (Kofler M, 2003).

Traditionally, CSPs are demonstrated most clearly within the distal muscles of the hand and forearm and less likely within the more proximal muscles of the arm, most specifically those muscles most associated with the withdrawal of the limb (Eckert NR et al., 2016;Inghilleri M,Cruccu G,Argenta M,Polidori L and Manfredi M, 1997;Leis A,Stokic D,Fuhr P,Kofler M,Kronenberg M,Wissel J,Glocker F,Seifert C and Stetkarova I, 2000;Serrao M et al., 2001). However, the evidence presented in earlier studies as well as replicated within the current study demonstrate that CSPs can be demonstrated within these withdrawal muscles (Eckert NR,Poston B and Riley ZA, 2018). The differences between these accounts with the previous literature may reside in the design setup however the clarity of the CSP existence within withdrawal muscles suggests a level of complexity not addressed fully within the current literature base. Therefore, the data demonstrates the need for a refinement in the traditional understanding of the CSP and its role within complex reflexive actions.

When pairing the CSP response with MEP data from TMS stimulation of the motor cortex we find that MEP suppression is greatest within the distal muscles of the hand and forearm, supporting previous accounts (Kofler M, 2004). Suppression of the conditioned MEPs was expected within the distal muscles (Abbruzzese G et al., 2001;Farina S,Valeriani M,Rosso T,Aglioti S,Tamburin S,Fiaschi A and Tinazzi M, 2001;Inghilleri M,Cruccu G,Argenta M,Polidori L and Manfredi M, 1997;Kofler M, 2003;Kofler M et al., 2008;Le Pera D,Graven-Nielsen T,Valeriani M,Oliviero A,Di Lazzaro V,Tonali PA and Arendt-Nielsen L, 2001;Rothwell JC et al., 1991;Serrao M,Parisi L,Pierelli F and

Rossi P, 2001;Serrao M,Pierelli F,Don R,Ranavolo A,Cacchio A,Curra A,Sandrini G,Frascarelli M and Santilli V, 2006), however it was unknown what the more proximal muscles of the upper-limb would present in the presence of noxious stimuli. The conditioned MEPs were facilitated when compared with the amplitude of the standalone MEP within proximal muscles, with the inverse effect seen within the distal muscles. Two possibilities exist that may suggest as to why this facilitated effect occurred. First, it may be due to the flexibility seen within the discharging of cortico-motoneuronal cells. Previous reports have demonstrated differences within TMS-induced peaks during periods of muscle co-contraction (Aimonetti J-M and Nielsen JB, 2002;Nielsen J et al., 1993). Within the current study, it remains a possibility that the co-contraction of the gripping muscles during the activation of the posterior deltoid muscle lead to an increase within cortical excitability inhibiting or “over-riding” the inhibitory reflex circuitry. Co-contraction of these muscles remains a possibility within all the tested muscles, as the grip was needed to be maintained in order to allow for the upper arm muscles to adequately contract for the study. However, this result was not seen within the other flexor muscles. Secondly, and more likely, there is a level of differential control when comparing distal to proximal muscles. This would be in agreement with the structural association of fewer direct cortico-motoneuronal connections in the shoulder. Although, it remains a possibility that this differential control is not a direct result of the amount of connections, but rather due to the influence of the cortico-motoneuronal connections on a particular muscle. It is well known that direct excitatory inputs to motoneurons from descending pathways to the muscles of the upper portion of the arm are characterized to have small excitatory post-synaptic potentials that fail to produce muscle contraction on their own (Baldissera F et al., 1981;Lemon RN, 2008;Lemon RN et al., 2004). This is not the case within the distal muscles of the hand and fingers (Porter R and Lemon R, 1993). Calculations have suggested that the total cortico-motoneuronal input to motoneurons supplying the wrists extensor muscle could potentially provide up to 60% of the facilitatory drive needed to maintain a motor unit discharge (Cheney PD et al., 1991). This provides evidence to suggest that the direct influence of the cortico-motoneuronal connections within the distal muscles of the hand and forearm is considerably greater than that of the proximal muscles. Therefore, a direct, strong inhibitory action on these

connections would produce pronounced inhibition. All hypothesized aside, the CSP remains a protective reflex that, according to the presented data, may serve to inhibit all muscle activity in response to noxious input. This inhibition within all muscles is implied to occur in an organized manner, as to enforce the exploration of an environment with the upper-limb. The inhibition of the distal muscles in the hand and forearm allows for control over the grip but similar inhibition of the upper arm and shoulder would not allow for withdrawal of the limb. In any case, the evidence presents a strong indication that a differential level of inhibitory control exists across the muscles of the upper-limb that serve to meet the functional requirements necessary to protect the upper-limb in the presence of noxious and/or painful stimuli.

Strengths and Limitations

The data presented within the current study provide a unique look at the level of complexity found within the organization of peripheral noxious input within the spinal cord. While the data is compelling it is necessary to note several key limitations. Initially it must be noted that the data presented within the current study is only applicable to young, healthy participants. While inferences can be made, direct application cannot be extended further into older or clinical populations. Additionally, it must be noted that the data does contradict previous accounts on the CSP, specifically the presence of the CSP within traditional “withdrawal” muscles. This may be due to the specific design/setup of the muscular contractions within the presented study as it did not truly isolated individual muscle contractions and could only provide limited control over the limb movement. It remains plausible that a greater level of limb control could elicit differing results. However, the results that were presented remain relatively straightforward and the study gains strength from the number of stimuli presented, all of which provided clear CSP data. This clarity within the data allowed for easy individualized, visual inspection and determination of the CSP and MEP within the data for all muscles recorded by the investigators.

Conclusions

Previous investigations have demonstrated the effectiveness of the CSP as a protective mechanism. However, to date, the extent as to how this reflex is organized has been up for debate. The current study has clearly demonstrated the existence of a distal to proximal relationship with a differential level of inhibitory control across the muscles of the upper-limb for the CSP. The results of the present study fall directly in line with previous theories as to the level of control needed to complete complex and manipulative movements within the distal muscles of the hand, and are most likely supported through the structural findings of the direct cortico-motoneuronal connections within the corticospinal tract. Nevertheless, the precise mechanisms of the CSP remain unclear but the present study provides a refinement within the current understanding of the spinal organization associated with the processing of noxious input. This in turn has provided direct evidence to suggest that the CSP response is the culmination of a complex network of interactions in response to peripheral nociceptive input.

References

- Abbruzzese G, Marchese R, Buccolieri A, Gasparetto B, Trompetto C (2001), Abnormalities of sensorimotor integration in focal dystonia. A transcranial magnetic stimulation study 124:537-545.
- Aimonetti J-M, Nielsen JB (2002), Cortical excitability and motor task in man: an investigation of the wrist extensor motor area. *Experimental brain research* 143:431-439.
- Baldissera F, Hultborn H, Illert M (1981), Integration in spinal neuronal systems. *Comprehensive Physiology*.
- Caccia G, Violini A (1973), [Current trends in the treatment of esophageal atresia]. *Minerva Med* 64:4884-4890.
- Caccia MR, McComas AJ, Upton AR, Blogg T (1973), Cutaneous reflexes in small muscles of the hand. *J Neurol Neurosurg Psychiatry* 36:960-977.
- Cheney PD, Fetz EE, Mewes K (1991), Neural mechanisms underlying corticospinal and rubrospinal control of limb movements. *Progress in brain research* 87:213-252.
- Criswell E (2010) *Cram's introduction to surface electromyography*. Jones & Bartlett Publishers.
- Eckert NR, Poston B, Riley ZA (2016), Modulation of the cutaneous silent period in the upper-limb with whole-body instability. *PloS one* 11:e0151520.
- Eckert NR, Poston B, Riley ZA (2018), Differential processing of nociceptive input within upper limb muscles. *PLoS One* 13:e0196129.
- Farina S, Valeriani M, Rosso T, Aglioti S, Tamburin S, Fiaschi A, Tinazzi M (2001), Transient inhibition of the human motor cortex by capsaicin-induced pain. A study with transcranial magnetic stimulation. *Neuroscience Letters* 314:97-101.
- Floeter MK, Gerloff C, Kouri J, Hallett M (1998), Cutaneous withdrawal reflexes of the upper extremity. *Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine* 21:591-598.
- Garnett R, Stephens JA (1980), The reflex responses of single motor units in human first dorsal interosseous muscle following cutaneous afferent stimulation. *J Physiol* 303:351-364.

Inghilleri M, Cruccu G, Argenta M, Polidori L, Manfredi M (1997), Silent period in upper limb muscles after noxious cutaneous stimulation in man. *Electroencephalogr Clin Neurophysiol* 105:109-115.

Kofler M (2003), Functional organization of exteroceptive inhibition following nociceptive electrical fingertip stimulation in humans. *Clin Neurophysiol* 114:973-980.

Kofler M (2004), Influence of transcutaneous electrical nerve stimulation on cutaneous silent periods in humans. *Neurosci Lett* 360:69-72.

Kofler M, Glocker FX, Leis AA, Seifert C, Wissel J, Kronenberg MF, Fuhr P (1998), Modulation of upper extremity motoneurone excitability following noxious finger tip stimulation in man: a study with transcranial magnetic stimulation. *Neuroscience Letters* 246:97-100.

Kofler M, Leis AA, Valls-Solé J (2019), Cutaneous silent periods–part 1: update on physiological mechanisms. *Clinical Neurophysiology*.

Kofler M, Valls-Sole J, Fuhr P, Schindler C, Zaccaria BR, Saltuari L (2008), Sensory modulation of voluntary and TMS-induced activation in hand muscles. *Exp Brain Res* 188:399-409.

Le Pera D, Graven-Nielsen T, Valeriani M, Oliviero A, Di Lazzaro V, Tonali PA, Arendt-Nielsen L (2001), Inhibition of motor system excitability at cortical and spinal level by tonic muscle pain. *Clinical Neurophysiology* 112:1633-1641.

Leis A, Stokic D, Fuhr P, Kofler M, Kronenberg M, Wissel J, Glocker F, Seifert C, et al. (2000), Nociceptive fingertip stimulation inhibits synergistic motoneuron pools in the human upper limb. *Neurology* 55:1305-1309.

Lemon RN (2008), Descending pathways in motor control. *Annu Rev Neurosci* 31:195-218.

Lemon RN, Kirkwood PA, Maier MA, Nakajima K, Nathan P (2004) Direct and indirect pathways for corticospinal control of upper limb motoneurons in the primate. In: *Progress in Brain Research*, vol. Volume 143 (Shigemi Mori DGS, Mario W, eds), pp. 263-279. Elsevier.

Nielsen J, Petersen N, Deuschl G, Ballegaard M (1993), Task-related changes in the effect of magnetic brain stimulation on spinal neurones in man. *The Journal of Physiology* 471:223-243.

Porter R, Lemon R (1993) *Corticospinal function and voluntary movement*. Oxford University Press, USA.

Rothwell JC, Thompson PD, Day BL, Boyd S, Marsden CD (1991), Stimulation of the human motor cortex through the scalp. *Experimental Physiology* 76:159-200.

Serrao M, Parisi L, Pierelli F, Rossi P (2001), Cutaneous afferents mediating the cutaneous silent period in the upper limbs: evidences for a role of low-threshold sensory fibres. *Clinical Neurophysiology* 112:2007-2014.

Serrao M, Pierelli F, Don R, Ranavolo A, Cacchio A, Curra A, Sandrini G, Frascarelli M, et al. (2006), Kinematic and electromyographic study of the nociceptive withdrawal reflex in the upper limbs during rest and movement. *J Neurosci* 26:3505-3513.

Švilpauskaitė J, Truffert A, Vaičienė N, Magistris MR (2006), Electrophysiology of small peripheral nerve fibers in man. A study using the cutaneous silent period. *Medicina (Kaunas)* 42:4.

Uncini A, Kujirai T, Gluck B, Pullman S (1991), Silent period induced by cutaneous stimulation. *Electroencephalogr Clin Neurophysiol* 81:344-352.

Wolpert DM, Flanagan JR (2001), Motor prediction. *Current biology* 11:R729-R732.