Applied Physiology, Nutrition, and Metabolism
 Physiologie appliquée, nutrition et métabolisme

**On Task: Considerations and Future Directions for Studies
 of Corticospinal Excitability in Exercise Neuroscience and
 Related Disciplines**

Journal:	<i>Applied Physiology, Nutrition, and Metabolism</i>
Manuscript ID	apnm-2018-0123.R1
Manuscript Type:	Review
Date Submitted by the Author:	19-Apr-2018
Complete List of Authors:	Kalmar, Jayne; Wilfred Laurier University,
Keyword:	corticospinal excitability, task-dependent, transcranial magnetic stimulation, spinal excitability, cortical excitability
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Title: On Task: Considerations and Future Directions for Studies of Corticospinal Excitability
in Exercise Neuroscience and Related Disciplines

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Draft

14 ABSTRACT:

15 Over the last few decades, transcranial magnetic stimulation (TMS) has emerged as a
16 conventional laboratory technique in human neurophysiological research. Exercise
17 neuroscientists have used TMS to study central nervous system contributions to fatigue, training,
18 and performance in health, injury, and disease. In such studies, corticospinal excitability is often
19 assessed at rest or during simple isometric tasks with the implication that the results may be
20 extrapolated to more functional and complex movement outside of the laboratory. However, the
21 neural mechanisms that influence corticospinal excitability are both state- and task-dependent.
22 Furthermore, there are many sites of modulation along the pathway from the motor cortex to the
23 muscle; a fact that is somewhat obscured by the all-encompassing and poorly-defined term
24 “corticospinal excitability.” Therefore, the tasks we use to assess corticospinal excitability and
25 the conclusions that we draw from such a global measure of the motor pathway must be taken
26 into consideration. The overall objective of this review is to highlight the task-dependent nature
27 of corticospinal excitability and the tools used to assess modulation at cortical and spinal sites of
28 modulation. By weighing the advantages and constraints of conventional approaches to studying
29 corticospinal excitability, and considering some new and novel approaches, we will continue to
30 advance our understanding of the neural control of movement during exercise.

31 **Keywords:** corticospinal excitability, task-dependent, transcranial magnetic stimulation, spinal
32 excitability, cortical excitability

33 INTRODUCTION:

34 Volitional movement requires input from many parts of the motor system, including
35 cortical motor areas (prefrontal cortex, premotor cortex, supplementary motor area, primary
36 motor cortex), subcortical structures (cerebellum, basal ganglia), and extrapyramidal tracts
37 arising from the brainstem, that is integrated with sensory input at both segmental and
38 supraspinal levels. Ultimately, however, the voluntary command to contract muscle is executed
39 by corticospinal motor neurons, which input to the spinal motor neurons that activate skeletal
40 muscle. Over the last three decades, transcranial magnetic stimulation (TMS) has been used to
41 assess the excitability of this motor pathway from motor cortex to skeletal muscle under a variety
42 of conditions. In the relatively new discipline of Exercise Neuroscience, TMS has been used to
43 identify fatigue-associated changes in this motor pathway (for review, see Gruet et al. 2013),
44 sex- and age-related differences in this fatigability (e.g. Yoon et al. 2015), training-induced
45 plasticity (for review, see Kidgell et al. 2017) of the central nervous system, and corticospinal
46 plasticity following brain injuries such as stroke (e.g. Knorr et al. 2011) and concussion (e.g.
47 Lefebvre et al. 2015). These studies report changes in what is typically referred to as
48 *corticospinal excitability* during a variety of simple and reproducible motor tasks.

49 Although the expression *corticospinal excitability* is being used more widely now, a clear
50 definition of this phrase is seldom presented. While this catch-all phrase may be the most
51 appropriate way to convey findings that cannot be isolated to a single mechanism along the
52 pathway from motor cortex to corticospinal motor neuron, to alpha motor neuron, to muscle fibre
53 to recording electrode, incautious use of the phrase may result in vague and easily misconstrued
54 statements of key findings. In a PubMed search of scientific publications, the term *corticospinal*
55 *excitability* first appears in 1994 (Brouwer and Ambury 1994, Werhahn et al. 1994), nearly a

decade after the first paper to describe transcranial magnetic stimulation was published by Barker et al., in The Lancet in 1985 (Barker et al. 1985). The temporal relationship between the emergence of TMS methodology in scientific literature and use of the term *corticospinal excitability* is probably not coincidental, and it seems likely that increased use of this phrase arose to accommodate TMS methodology. Wehrman et al., (1994) first used the phrase in 1994, but only once in the manuscript to state that coil orientation could be used to isolate “changes in corticospinal excitability to a cortical level”, implying that the term *corticospinal excitability* referred to the net of cortical and spinal mechanisms. As usage of the phrase increased over the next thirty years, the implied definition became more diffuse and arguably more problematic when it became synonymous with *any* change in the evoked potential recorded in the muscle. For the purposes of this review, the term *corticospinal excitability* reflects the excitability of the pathway between the corticocortical motor axons depolarized by the magnetic stimulus and spinal motor neurons that innervate the muscle of interest, and encompasses the cortical and spinal origins of changes in the evoked potential only when changes in peripheral transmission are ruled out or accounted for. This terminology (Table 1), reflects the constraints of the tools that we use to study the system rather than distinct and easily-defined neurophysiological mechanisms.

Corticospinal excitability: What does single-pulse TMS measure?

When discharged over the primary motor cortex (M1), a single suprathreshold TMS stimulus (Figure 1, site A) depolarizes the axons of corticocortical neurons to synaptically activate corticospinal motor neurons and elicit a series of descending volleys (reviewed by Bestmann and Krakauer 2015). The response to this stimulus, the motor evoked potential (MEP), is recorded in the contralateral target muscle using surface electromyography (Figure 1,

79 trace a1). The latency of this TMS-evoked potential suggests that TMS preferentially excites
80 monosynaptic corticospinal projections to the spinal motor neuron pool (Bestmann and Krakauer
81 2015). Given that the MEP is elicited by synaptic input to corticospinal motor neurons and
82 recorded in the muscle, this evoked potential is the net effect of cortical, spinal, and peripheral
83 neuromuscular transmission. At a cortical level, the response to the stimulus will be dependent
84 upon synaptic efficacy of the corticocortical neurons, which are depolarized by the stimulus and
85 input to corticospinal motor neurons, the intrinsic excitability of the corticospinal motor neurons
86 that receive the corticocortical motor neuron input, and the net excitatory and inhibitory input to
87 the corticospinal motor neuron. These factors will determine the strength of the descending
88 volley transmitted to the spinal motor neuron pool. Assuming that corticospinal axonal
89 transmission failure is not a consideration, the descending volley will activate a portion of the
90 motor neuron pool that is contingent upon the efficacy of corticospinal synaptic transmission, the
91 intrinsic excitability of the spinal motor neuron, and net effect of inhibitory and excitability
92 segmental and propriospinal inputs, and neuromodulatory and ionotropic descending inputs.
93 Changes at any of these cortical and spinal sites could alter the amplitude of the resultant MEP
94 and would thus contribute to what could reasonably be referred to as *corticospinal excitability*,
95 however, the recording of the electrical response in the target muscle (the MEP) is also
96 dependent on peripheral transmission which may be altered at the neuromuscular junction, along
97 the sarcolemma, and between the muscle and recording electrode. Thus, if the single-pulse
98 MEP is to be used as a global measure of “corticospinal” excitability, peripheral transmission
99 must be taken into account (Kalmar and Cafarelli 2004). This is most often achieved by
100 recording the maximal compound muscle action potential, or M wave (Figure 1, trace e)
101 responses elicited via peripheral nerve stimulation (Figure 1, site E). Changes in the MEP that

occur in the absence of changes in the M wave may be attributed to events upstream to the point of peripheral nerve stimulation, as a consequence of either cortical or spinal modulation.

Assessing cortical contributions to corticospinal excitability

Several approaches are used to identify a cortical origin, or at least a supraspinal origin, in TMS studies of fatigue, training, injury, aging, and pathology. The first approach is to compare the MEP elicited by a single pulse of TMS to some measure of spinal excitability derived from a potential evoked by stimulation further down the motor pathway such as the cervicomedullary evoked potential (CMEP) or the H reflex (Figure 1, traces c and d). For example, fatigue is attributed to a supraspinal mechanism when MEPs elicited with single-pulse TMS decline, but CMEPs do not (Yacyshyn et al. 2017). Similarly, the effect of limb position on corticospinal excitability may be attributed to supraspinal or spinal mechanisms by reporting relative changes in MEP and CMEP. For example, biceps brachii MEP/Mwave increases and CMEP/Mwave remains unchanged at 90° shoulder flexion compared to 0° when the muscle is at rest. However, the same change in joint angle elicits a decrease in both MEP/M wave and CMEP/Mwave when the muscle is slightly active (Collins et al. 2017). In this case, the relative changes in MEP and CMEP suggest that changes in limb position alter corticospinal excitability through a predominantly supraspinal mechanism at rest and a spinal mechanism when the muscle is active. The spinal measures that are typically compared to a single-pulse MEP are described in detail in the following section.

Paired-pulse TMS is also used to identify intracortical mechanisms of corticospinal excitability. Briefly, two pulses are applied over the primary motor cortex through the same coil (Figure 1, site B). In the original paired-pulse paradigm (Kujirai et al. 1993), the first pulse or

the “conditioning stimulus” is subthreshold and does not, delivered alone, produce an MEP in the target muscle. The second pulse, or the “test pulse”, is suprathreshold and does produce an MEP. The time between the two stimuli determines the effect of the conditioning stimulus on the test stimulus (Kujirai et al. 1993). When the interstimulus interval is less than 5 ms, the peak-to-peak amplitude of the conditioned MEP (Figure 1, trace b, red) is smaller than that of the unconditioned test MEP. This effect is referred to as short interval intracortical inhibition (SICI). When the interstimulus interval is 10-15 ms, the peak-to-peak amplitude of the conditioned MEP (Figure 1, trace b, green) is greater than that of the unconditioned test MEP. This effect is referred to as intracortical facilitation (ICF). Other paired-pulse paradigms utilize suprathreshold conditioning pulses to assess other intracortical circuits, including long interval intracortical inhibition (LICI) which is elicited with an interpulse interval between 50 and 200ms, and interhemispheric inhibition (IHI) which is elicited by a conditioning stimulus to the opposite hemisphere 6 - 50 ms prior to the test pulse (for review, see Reis et al. 2008).

A third approach to identifying changes in cortical excitability, is to use a single suprathreshold TMS pulse to record the cortical silent period (Chen et al. 1999) which follows an MEP during a voluntary muscle contraction (Figure 1, trace a2). This period of electrical silence is due in part to spinal mechanisms, however, there is sufficient evidence from pharmacological and paired-pulse TMS studies of SICI and LICI to suggest that the later part of the silent period evoked with TMS does have a cortical component (Reis et al. 2008). Accordingly, this cortical silent period provides insight into intracortical inhibition during voluntary activation.

While several experimental approaches provide strong support of an intracortical origin for paired-pulse conditioning and the cortical silent period, the specific mechanisms (proposed

circuitry, suggested interneuronal populations, and role of various neurotransmitters) are much more speculative than implied in many discussions of key findings in TMS research. Thus, the proposed mechanisms of paired-pulse TMS and the cortical silent period should be considered as a very useful conceptual framework, but one that must nonetheless be applied with caution as clearly noted by those who propose them (for review see Reis et al. 2008).

Assessing spinal contributions to corticospinal excitability

There are a number of experimental approaches used to assess the spinal component of changes in corticospinal excitability. A more detailed description of the methodologies, advantages, and limitations of these conventional measures of motor neuron excitability are reviewed thoroughly by McNeil et al. (2013). The most common measures of spinal excitability in studies of corticospinal excitability include the Hoffman reflex (H reflex) and cervicomedullary evoked potentials (CMEP). In each case, the objective is to determine spinal motor neuron responsiveness to a stimulus that depolarizes the axon of a neuron with monosynaptic input to the spinal motor neuron pool. In the case of the H reflex, the axons of large diameter afferents are depolarized via percutaneous electrical stimulation of the mixed nerve (Figure 1, site D). In the case of the CMEP, descending corticospinal axons are the targets of transmedullary electrical or magnetic stimulation (Figure 1, site C). Both approaches are used to assess the spinal component of corticospinal excitability, although in each case there are a few underlying assumptions that should not be dismissed (reviewed by Knikou 2008, McNeil et al. 2013). The H reflex (Figure 1, trace d) is elicited by percutaneous stimulation of the mixed nerve using a pulse duration that is longer (typically 1 ms) and of a lower intensity than that required to directly activate motor axons and produce an M wave (Figure 1, trace e). This low-intensity, long-duration stimulus preferentially depolarizes the larger diameter Ia afferents

(Figure 1, site D) of the mixed nerve which monosynaptically excite the homologous spinal motor neuron pool. The proportion of the homologous spinal motor neuron pool activated by the afferent volley will depend on the overall excitability of the motor neurons (net effect of excitatory and inhibitory inputs as well the intrinsic excitability of the neuron) and is reflected by the peak-to-peak amplitude of the long latency H reflex. The peak-to-peak amplitude of the H reflex is plotted over a range of stimulus intensities and the maximal H reflex ($H_{\max}$, normalized to the maximal M wave) or the slope of the ascending limb of the H reflex recruitment curve (H_{slope} , normalized to the slope of the M wave curve) are used as measures of spinal excitability. The $H_{\max}$ approach is advantageous in that it provides a quick measure made in between contractions or during low-level contractions during the fatigue protocol. The downside of this approach is that a single H reflex reflects the excitability of a very narrow portion of the motor neuron pool that is not likely the same as that reflected by the cortically-evoked MEP to which it may be compared. While the H_{slope} approach provides an estimate of the excitability of a much bigger proportion of the motor neuron pool, it can take upwards of 3 minutes to generate a carefully constructed H reflex recruitment curve during which time considerable recovery from fatigue will take place.

H reflex estimates of spinal excitability are influenced by presynaptic inhibition, are not entirely monosynaptic, and are difficult to elicit in proximal muscles of the lower limb and in the upper extremity (Knikou 2008). Consequently, cervicomedullary-evoked potentials (CMEP) (Figure 1, trace c) elicited via transmastoid magnetic or electrical stimulation (Figure 1, site C) have frequently been described as the “most appropriate” means to assess the spinal component of corticospinal excitability in TMS studies (Taylor and Gandevia 2004). This view is based on two key assumptions. The first is that stimulation of the brainstem at the transmastoid level

(above the origin of the propriospinal interneurons at C3-C4) activates primarily corticospinal axons from amongst the other descending and ascending tracts. The second assumption is that the CMEP represents a predominantly monosynaptic input that, unlike the H reflex, is not subject to presynaptic inhibition (Nielsen and Petersen 1994). While there is strong evidence from collision experiments and post-stimulus time histograms of single unit responses to support these assumptions (at least in the upper limb), it is important to note that other forms of stimulation at the same site, albeit with different stimulation parameters, have been used to assess vestibular and cerebellar contributions to motor output. Furthermore, transmastoid stimulation may excite axons of spinal motor neurons of the ventral roots if the stimulation intensity is high or the stimulus is not delivered in the optimal location. If this occurs, the resultant CMEP no longer provides an estimate of spinal motor neuron excitability. While this error can be avoided by carefully monitoring latencies, these data are not always reported. These caveats and considerations are reviewed in greater depth by Taylor and Gandevia (2004). Finally, like the H reflex, the portion of the motor unit pool represented by the CMEP may not be the same as that which contributes to the cortically-evoked MEP given that the CMEP reflects a single descending volley and TMS-elicited MEP is comprised of multiple descending volleys (Day et al. 1987).

Both the H reflex and the CMEP provide a measure of “net excitability” of the motor neuron pool that is determined by the summation of excitatory and inhibitory descending and afferent input as well as intrinsic motor neuron excitability. While intrinsic motor neuron excitability is frequently cited as a mechanism that may contribute to the modulation of the H reflex and CMEP, it is rarely noted that the intrinsic excitability of a spinal motor neuron at rest is quite different from the excitability of a neuron near threshold and during rhythmic firing.

216 Neuromodulatory drive is a significant contributor to motor output, setting spinal motor neuron
217 excitability according to both state and task through the generation of persistent inward currents
218 (PIC) in motor neuron dendrites (Heckman et al. 2009). PIC amplifies and prolongs the effects
219 of synaptic input to increase firing rate and prolong the output of spinal motor neurons via
220 voltage-dependent sodium and calcium conductances, but only when the neuron is near or at
221 threshold (Gorassini et al. 2002). As such, measures of corticospinal excitability such as the H
222 reflex and CMEP made with the muscle at rest, do not take this important determinant of motor
223 neuron excitability into account. Even when delivered during muscle activation, brief stimuli
224 such as those used to elicit an H-reflex or CMEP may activate the faster sodium conductance,
225 but would not activate the slower and longer-lasting calcium conductances that contribute most
226 significantly to PIC (Heckman et al. 2009).

227 It is possible to estimate the amplitude of PIC that contributes to the intrinsic excitability of
228 human spinal motor neurons using intramuscular electromyography to record the firing behavior
229 of motor unit pairs (Figure 1, trace f) (Gorassini et al. 2002, Vandenberg and Kalmar 2014). To
230 obtain an estimate of PIC, the firing frequency of a low-threshold “control” motor unit is used as
231 a proxy measure of synaptic input to the spinal motor neuron pool during a triangular ramp
232 contraction. As the participant traces the ascending limb of the ramp, more synaptic input is
233 required to generate the required motor output, as indicated by an increase in control motor unit
234 firing rate (Figure 1, plot g,). Persistent inward current is then estimated from a higher-
235 threshold “test” motor unit recruited later in the ramp. If this test unit did not have a PIC as a
236 source of intrinsic excitability, then one would expect it to be recruited (start firing) and
237 derecruited (stop firing) at the same level of “synaptic input” (or the same control-unit firing rate,
238 since this is our proxy measure of synaptic input). In contrast, motor units with a PIC have

greater intrinsic excitability and can continue firing with less synaptic input once they are activated. Consequently, the control-unit firing rate (our estimate of synaptic input) will be lower at test unit decruitment than at recruitment. This difference in control-unit firing rate at test unit recruitment and decruitment (ΔF) provides an estimate of PIC amplitude in the test motor unit. This method does rest heavily on several assumptions (e.g. shared synaptic input, saturation of PIC in the control unit prior to test unit recruitment, and a control unit firing range which is not saturated during the ramp) which must be tested in order to include the control and test motor unit pairs in analysis (Stephenson and Maluf 2011). Furthermore, ramps with slower rates of rise and longer durations will result in ΔF values that are due to intrinsic properties other than PIC that contribute to nonlinear firing behaviour (Revill and Fuglevand 2011, Vandenberg and Kalmar 2014). Paired motor unit recordings do *not* provide quick and easy estimates of intrinsic motor neuron excitability. Nonetheless, intrinsic properties such as PIC contribute significantly to spinal motor neuron output, and paired motor unit recordings provide a means to assess task-dependent modulation of corticospinal excitability that is intrinsic to the spinal motor neuron that is not evident at rest and not fully revealed by the brief stimuli that elicit the CMEP and H reflex. For example, it is possible that increased monoaminergic drive during fatiguing exercise may elicit an increase in intrinsic motor neuron excitability that compensates for both other sites of corticospinal hypoexcitability and muscle contractile failure that accompany fatigue. This hypothesis has not yet been tested.

Corticospinal Excitability is State-, Time-, and Task-dependent

Changes in corticospinal excitability reflected by the MEP may be due to both cortical and spinal mechanisms. The relative extent to which these intracortical and segmental interactions modulate MEP amplitude will depend on the state (e.g rest, arousal, fatigue, attention, injured,

262 trained) as well as the task (e.g. rest, isometric contraction, isotonic, locomotor, required
263 precision). Furthermore, corticospinal excitability is not static during a motor task. It changes
264 rapidly leading up to, during, and after movement (Chen and Hallett 1999) such that TMS
265 provides a measure of corticospinal excitability only at the time of stimulation. Therefore, the
266 task, the state, and timing of the stimulus should be considered when designing experiments,
267 interpreting the results, and applying significant findings to behaviours that extend beyond those
268 studied. Although considering task is important in any study of the neural control of movement,
269 the ensuing discussion will largely focus on the task-dependent modulation of corticospinal
270 excitability during fatigue.

271 Ideally, we would assess corticospinal excitability (preferably at both cortical and spinal
272 levels) during the very motor tasks that we are most interested in, and we would make these
273 measures in multiple muscles; those that we believe to be most relevant to the task, and those
274 that are not likely to contribute to the task (to achieve some measure of specificity of changes in
275 corticospinal excitability). Furthermore, given that TMS provides a measure of corticospinal
276 excitability only at the time of stimulation, we would ideally assess it across a range of time
277 points that reflect the planning or execution phases of motor output that we contend to be most
278 pertinent to the questions that we pose. Of course, it is not possible to accomplish all of this in a
279 single experiment. Instead, corticospinal excitability is typically assessed with the muscle at
280 rest, or during visually-guided contractions at a target level of muscle activation, often in a
281 muscle operating across a single joint with movement at the joint above and below restricted or
282 completely restrained. Use of these controlled and reproducible laboratory protocols is easily
283 justified, but these paradigms do nonetheless deviate from the motor tasks and behavioural states
284 outside the lab that we are generally interested in understanding. By considering the advantages

and limitations of the experimental task and the timing of stimuli used to measure corticospinal excitability during the task, it is possible to design experiments that more closely approximate the “real-life” motor tasks we ultimately wish to understand.

Resting measures of corticospinal excitability:

The advantage of recording corticospinal excitability at rest is that it is easier to identify and control for unintended changes in muscle activation of agonists, synergists, or antagonists that would confound the interpretation of the results. However, measurements made at rest without a plan to contract are measurements made in a non-motor state and it has been noted, sometimes as an afterthought, that measurements of corticospinal excitability made in relaxed muscle may not reflect corticospinal excitability during voluntary contraction. A stronger stance on this issue is probably warranted. The resting motor evoked potential provides a measure of transmission from brain to muscle with very different muscle afferent input (e.g. GTO, spindle), and potentially very different joint and cutaneous input that would arise from force production and/or limb movement. Furthermore, a motor evoked potential elicited at rest with no plan to contract provides a measure of transmission from brain to muscle with very different input to the primary motor cortex and different descending corticospinal drive, extrapyramidal ionotropic and neuromodulatory input, and propriospinal inputs to the spinal motor neuron. Thus, changes in corticospinal excitability observed at rest with no plan to contract are not necessarily relevant during a motor task given that segmental and descending inputs may compensate for (or contribute to) changes in resting excitability once a motor task is initiated. A good solution would then be to assess corticospinal excitability during a contraction.

Assessing corticospinal excitability during contractions:

Not only are potentials evoked during muscle contractions reflective of a motor state, but the variability of the evoked potentials is considerably reduced as muscle activation increases (Darling et al. 2006), thus enhancing statistical power. Furthermore, motor threshold (the minimum amount of stimulator output required to elicit evoked potentials 50% of the time) is lower during voluntary contraction than at rest. This means that a lower stimulation intensity may be employed, thus making the protocol more comfortable for the participant. What, then, are the limitations of assessing corticospinal excitability during a muscle contraction? While there are no disadvantages that preclude the effective use of this approach, there are factors that should be taken into account, including the intensity and the nature of the contraction. Differences in these factors may explain divergent results in otherwise similar studies and limit the extrapolation of the findings to all but similar motor tasks.

Consider a protocol that assesses corticospinal excitability during a submaximal contraction of a muscle maintained at a target presented to the participant as EMG or force output to be traced or maintained on a computer monitor. The idea, quite reasonably, is to control muscle activation and joint angle to permit consistent comparisons within and between experiments. However, this is a visuomotor task that requires some precision; a laboratory task that is significantly different from the movements required for most daily activities of living, sport performance, and occupational tasks to which we may wish to apply our findings. We do not normally have augmented feedback during motor tasks outside the lab; and within the lab, the nature of the feedback and the precision required to complete the task will affect measures of corticospinal excitability. For example, cortical activity is suppressed to a greater extent and for a longer time with visual feedback of finger position compared to visual feedback of the force output even when the mechanical requirements of the task and pre-stimulus muscle activation are

the same (Lauber et al. 2012). Furthermore, corticospinal excitability is increased when the difficulty of a force-matching task is made more difficult by increasing the sensitivity of the force transducer (Pearce and Kidgell 2009), and in precise target-matching contractions compared to power contractions (Schieppati et al. 1996). To further complicate the matter, cortical excitability and inhibition during simple finger abduction across a single isolated joint is not the same as during more natural manual tasks, such as pincer and power grip tasks and object exploration. For example, when paired-pulse TMS is used to assess cortical modulation during these different tasks, there is less SICI during a precision grip than during simple finger abduction and at rest, but no task-dependent effect on long-interval intracortical inhibition (Opie et al. 2015). When intracortical inhibition is assessed using the cortical silent period, intracortical inhibition is lowest during a power grip compared to a precision grip, and highest during simple finger abduction (Tinazzi et al. 2003). Finally, cortical silent periods are longest (the most inhibition) during a tactile exploration task, and shortest (the least inhibition) during a visually-guided ramp contraction, when compared to a tonic finger-abduction contraction (Hess et al. 1999). Clearly, we must consider the “task at hand” if we are to measure corticospinal excitability during muscle activation. As an aside, when acoustic startle is used to elicit reticular system input to both cortical and spinal motor neurons, MEPs are suppressed more during power grip than during precision and finger abduction (Tazoe and Perez 2017) which highlights the need to consider task-specific modulation of inputs other than the corticospinal tract during movement.

Assessing corticospinal excitability during a contraction held at a submaximal target poses additional challenges if the contractions are fatiguing. Experimental paradigms that elicit fatigue (intentionally or not) make it difficult to ensure that a cortical stimulation is applied at a

353 consistent level of muscle activation. In this case, the activation level required to maintain any
354 given force target may be altered by muscle contractile failure and subsequent increase in motor
355 unit recruitment (Bigland-Ritchie et al. 1986) whereas rectified or root-mean-square EMG
356 targets for muscle activation may be confounded by alterations in peripheral transmission
357 (Kalmar and Cafarelli, 2004). This matters because relatively small changes in muscle activation
358 level alter spinal motor neuron excitability and shifts the balance between cortical inhibitory and
359 facilitatory circuits (Ortu et al., 2008). Furthermore, an often-overlooked aspect of target-
360 matching fatigue protocols is that the nature of task itself may change as fatigue progresses and
361 alternative strategies are used to hold a target force. At the onset of a fatigue protocol, for
362 example, the motor task is to reach and hold a submaximal target (a visuomotor task that requires
363 some precision). If the endpoint (T_{lim}) for the fatigue protocol is defined as the inability to
364 reach and hold a target, then the motor task changes as T_{lim} approaches. The participant is no
365 longer reliant on visual feedback to produce and maintain a precise motor output. The task is
366 now to generate maximal or near maximal effort. In a recent investigation of the intracortical
367 mechanisms of fatigue, we noted that although intracortical facilitation declined over the first
368 75% of an intermittent submaximal isometric fatigue protocol, it was higher at the point of
369 failure (Sharples et al. 2016) when the participant could no longer maintain the target. In this
370 case, the task shifted from tracing a target using visual feedback to meet and maintain a precise
371 level of force at the onset of the protocol, to exerting a near maximal effort in an attempt to meet
372 the target force at the end of the protocol (a task that no longer requires precision). As such, the
373 nonlinear change in intracortical facilitation at the end of the protocol may have reflected a task-
374 dependent modulation (precision vs power) of cortical excitability rather than a state-dependent
375 modulation (fatigue). Fatigue-associated changes in intracortical facilitation were not a

consequence of increased muscle activation required to meet the target force in this experiment, because the intracortical facilitation was assessed with the muscle at rest just prior to the contraction thus avoiding the confounding effects of muscle activation.

Assessing corticospinal excitability at rest prior to a contraction

Excitability of the primary motor cortex changes before muscle activation, during movement preparation, and after contraction as sensory feedback returns to resting state (for review see Chen and Hallett 1999). Measuring corticospinal excitability at rest just before a planned contraction may be a good compromise between measuring corticospinal excitability at rest with no plan to contract (a non-motor state) and during contraction (when changes in muscle activation may confound the results). Furthermore, measurements of corticospinal excitability made prior to movement contribute to our understanding of the preparation phase of movement. We have previously assessed cortical excitability and interhemispheric inhibition in a 500-ms period prior to externally-cued, but rhythmically-repeated, force-matching contractions and found that cortical excitability and interhemispheric inhibition were both higher compared to at rest with no plan to contract (Sharples and Kalmar 2012). We then used the same pre-contraction protocol to assess intracortical mechanisms of fatigue and found increased ICF and decreased SICI prior to contractions at the point of task failure (Sharples et al. 2016). This approach provides a measure of corticospinal excitability in a motor state but without the confounding effects of muscle activation targets that may change over the course of an experiment that elicits neuromuscular fatigue. Nonetheless, both the timing of the stimulus and the nature of the planned contraction affect even pre-movement measures of corticospinal excitability. When the task is a simple reaction time task that requires the participant to contract

as quickly as possible after a “Go” signal, the MEP amplitude begins to increase approximately 80ms prior to movement. If the task is self-paced rather than externally-cued, the increase in MEP amplitude begins approximately 100ms prior to movement (Chen et al. 1998). A release of intracortical inhibition precedes this increase in corticospinal excitability (Reynolds and Ashby 1999), and when an externally-cued task requires the participant decide whether or not to contract, intracortical inhibition may play an even more significant role. For example, the amplitude of single-pulse MEPs in the agonist and antagonist muscles (Hoshiyama et al. 1997), and the homologous contralateral muscle to agonist are decreased after “no-go” commands in choice reaction time tasks (Leocani et al. 2000). This reduction in corticospinal excitability is attributed to enhanced SICI in the agonist muscle and a decreased LICI in agonist and surrounding muscles when contraction was withheld during “no-go” trials (Sohn et al. 2002). While these paired-pulse studies suggest that a cortical mechanism contributes to changes in corticospinal excitability leading up to movement execution (and suppression), premovement increases in corticospinal excitability also have a spinal component attributed largely to reductions in presynaptic inhibition (Eichenberger and Ruegg 1984).

Moving from conventional paradigms to natural motor tasks:

A great many studies of corticospinal excitability are conducted using upper limb muscles, most often recording evoked potentials from biceps brachii, first dorsal interosseous, and abductor pollicis brevis, and occasionally wrist flexors or extensors. However, the tasks performed by the upper limb are, of course, quite different from the tasks performed by the lower limb. Depending on the overall objectives and intended application of the study, the upper limb may indeed be the best model for understanding the role of corticospinal excitability in motor

420 function. On the other hand, assessing corticospinal excitability using a finger muscle, may not
421 provide much insight into the neural control of postural and locomotor tasks carried out by lower
422 limb musculature. While it is possible to assess corticospinal excitability using single-pulse
423 TMS in the lower extremities, it is more difficult due to the deep position of the leg region of the
424 motor cortex within the interhemispheric fissure compared to the lateral and superficial hand
425 region. Nonetheless, TMS is used to assess fatigue-associated changes in corticospinal
426 excitability in isometric contractions of lower limb muscles, most often in the quadriceps (e.g.
427 Kalmar and Cafarelli 2006, Temesi et al. 2014, Finn et al. 2018) and tibialis anterior (e.g. McKay
428 et al. 1995, McKay et al. 1996, Lentz and Nielsen 2002) which are more responsive to TMS than
429 medial gastrocnemius and soleus motor neurons (Brouwer and Ambury 1994). Recording
430 cortically-evoked potentials from these muscles during locomotion is even more challenging, but
431 it is possible. Such studies suggest that corticospinal excitability of ankle dorsiflexors and
432 plantarflexors is both task-dependent (visuomotor precision stepping compared to normal gait)
433 (Schubert et al. 1999) as well as phase-dependent (Knikou et al. 2013). More recently, the
434 corticospinal contributions to rhythmic “locomotor-like” activity have been studied in both lower
435 limb (Sidhu et al. 2012) and upper limb (Forman et al. 2015, Spence et al. 2016) cycling,
436 approaches which eliminate the technical challenges of eliciting cortically-evoked and
437 transmedullary-evoked potentials during treadmill walking. The development of arm cycling
438 protocols to investigate locomotor-like activity provide an excellent example of a functionally-
439 relevant laboratory task that circumvents the challenges of assessing corticospinal excitability in
440 lower limb muscles, but provides valuable insight into phase-dependent (Spence, Alcock et al.
441 2016), cadence-dependent (Forman et al. 2015), and workload-dependent (Spence et al. 2016)

modulation of corticospinal excitability during rhythmic and automated motor behavior characteristic of locomotion.

One of the arguments for using a conventional TMS paradigm, such as delivering pulses during isometric target-force contractions across a single joint, is that these protocols allow for consistent and reproducible experimental conditions during the delivery of the stimuli. However, when we perform natural motor tasks outside of the laboratory, there is considerable variability in the way we perform a task, because of our interactions with a changing environment and shifts in the strategies used to perform a task with fewer constraints. Accordingly, the variability that we seek to minimize in the laboratory is an important component of natural motor tasks. Designing experiments which systematically investigate this trial-to-trial variability in the performance of natural motor tasks will provide valuable insight into corticospinal modulation during movement.

Conclusion

Over the three decades since the first TMS article appeared in the Pubmed database, a great deal of effort has gone into studying the role that corticospinal excitability may play in the neural control of movement in health, disease, injury, aging, training, and fatigue in the discipline of exercise neuroscience. Conventional paradigms that assess cortical and spinal excitability at rest and during muscle activation have contributed significantly to our understanding of the neural control of muscle. However, an appreciation of the time- and task-dependent nature of corticospinal excitability should inspire us to continue devising novel and functionally relevant paradigms as we move forward. Just as importantly, more explicit discussion of the how our experimental tasks differ from volitional movement in a natural environment and the use of more

clearly defined terminology will help to ensure that our significant findings are not applied out of context.

Conflict of Interest:

The author has no conflicts of interest to report.

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Table 1: Definitions of Corticospinal Excitability, Cortical Excitability, and Spinal Excitability. Definitions of these commonly used terms are presented along with the evoked potentials most commonly used to assess excitability of the motor pathway in human exercise neuroscience studies.

	Definition	Most Common Measures*
Corticospinal Excitability	Excitability of the pathway from the cortical site of depolarization (axons of corticocortical motor axons) to the site of recording (muscle) that may be attributed to cortical and/or spinal mechanisms when neuromuscular transmission is taken into account.	MEP (when Mwave does not change) MEP/Mwave
Cortical Excitability	The responsiveness of corticospinal motor neurons to a cortical stimulus that may be attributed to the intrinsic excitability of the corticospinal motor neuron and its net excitatory and inhibitory inputs.	MEP/CMEP Intracortical Facilitation (ICF) Intracortical Inhibition (SICI, LICI) Cortical Silent Period (CSP)
Spinal Excitability	The responsiveness of spinal motor neurons to an afferent or descending monosynaptic input that may be attributed to its intrinsic excitability, and net excitatory and inhibitory descending and segmental inputs.	CMEP H reflex

*MEP, motor evoked potential; M wave, mass action potential; CMEP, cervicomedullary evoked potential; SICI, short interval intracortical inhibition; LICI, long interval intracortical inhibition; H reflex, Hoffman reflex.

632 **Figure Captions**

633

634 Figure 1: Sites of stimulation and corresponding evoked potentials most commonly used to
635 assess corticospinal excitability in exercise neuroscience studies. Sites for magnetic (blue coil)
636 and electrical (yellow bolt) stimulation are denoted with upper case letters together with the
637 evoked potentials (corresponding lower case letters) recorded using surface electromyography
638 (traces a to e). The MEP (a1) is elicited by single-pulse TMS (A) via depolarization of the axons
639 of corticocortical motor neurons that input to the corticospinal motor neuron (CS) to provide a
640 measure of corticospinal excitability when peripheral transmission, assessed through peripheral
641 nerve stimulation (E) to elicit an M wave (e), is taken into account. Changes in corticospinal
642 excitability may be due to cortical mechanisms or spinal mechanisms. Paired-pulse TMS (B) is
643 used to assess intracortical facilitation using a subthreshold conditioning pulse that precedes a
644 suprathereshold test pulse by 10 to 12 ms to increase the amplitude of the single-pulse MEP
645 (green trace in b). When the conditioning pulse precedes the test pulse by 1 to 3 ms, the single-
646 pulse MEP amplitude is suppressed providing a measure of intracortical inhibition (red trace in
647 b). A single-pulse suprathereshold pulse (A) elicited during voluntary activation elicits a cortical
648 silent period (a2) to provide another measure of intracortical inhibition. Spinal excitability is
649 assessed via transmedullary stimulation (C) of the axons of corticospinal motor neurons to elicit
650 a CMEP (c) or by stimulation of 1a afferent neurons of the mixed nerve (D) to elicit an H reflex.
651 These measures of spinal excitability are the net effect of excitatory and inhibitory inputs to
652 spinal motor neurons from the corticospinal tract as well as extrapyramidal inputs from the
653 brainstem (purple dashed lines, not all are shown) and propriospinal inputs (not shown), the
654 many afferent inputs to segmental circuitry (blue dashed lines, not all shown), and intrinsic
655 excitability of the spinal motor neuron (α MN). Persistent inward current is a key mechanism of

656 intrinsic motor neurons that cannot be assessed at rest using evoked potentials, but can be
657 estimated using intramuscular paired motor unit recordings (f) as the difference between control
658 unit firing rates (ΔF) at test unit recruitment and derecruitment (g).

Draft