Title: Variation of corticospinal excitability during kinesthetic illusion induced by musculotendinous vibration

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Abstract

Introduction

Despite being studied for >50 years, the neurophysiological mechanisms underlying vibration(VIB)-induced kinesthetic illusions are still unclear. The aim of this study was to investigate how corticospinal excitability tested by transcranial magnetic stimulation (TMS) is modulated during VIB-induced illusions.

Methods

Twenty healthy adults received vibration over wrist flexor muscles (80 Hz, 1 mm, 10 seconds). TMS was applied over the primary motor cortex representation of wrist extensors at 120% of resting motor threshold in four random conditions (10 trials/condition) : baseline (without VIB), 1s, 5s and 10s after VIB onset. Means of motor evoked potentiels (MEP) amplitudes and latencies were calculated.

Results

Statistical analysis found a significant effect of conditions (stimulation timings) on MEP amplitudes ($p=0.035$). Paired-comparisons demonstrated lower corticospinal excitability during VIB at 1s compared to 5s ($p=0.025$) and 10s ($p=0.003$), although none of them differed to baseline values.

Discussion

Results suggest a time-specific modulation of corticospinal excitability in muscles antagonistic to those vibrated, i.e. muscles involved in the perceived movement. An early decrease of excitability was observed at 1s followed by a stabilization of values near baseline at subsequent time-points. At 1s, the illusion is not yet perceived or not strong enough to up-regulate corticospinal networks coherent with the proprioceptive input. Spinal mechanisms, as reciprocal inhibition, could also contribute to lower the corticospinal drive of non-vibrated muscles in short period before the illusion emerges.

Conclusion

Our results suggest that neuromodulatory effects of VIB are likely time-dependent, and that future work is needed to further investigate underlying mechanisms.

KEYWORDS: Kinesthetic illusion, tendon vibration, transcranial magnetic stimulation, primary motor cortex

New & Noteworthy

1. The modulation of corticospinal excitability when perceiving a vibration (VIB)-induced kinesthetic illusion evolves dynamically over time.
2. This modulation might be linked to the delayed occurrence and progressive increase in strength of the illusory perception in the first seconds after VIB start.
3. Different spinal/cortical mechanisms could be at play during VIB, depending on the tested muscle, presence/absence of an illusion, and the specific timing at which corticospinal drive is tested per/post VIB.

Introduction

Musculotendinous vibration (VIB) is a peripheral neurostimulation method known to elicit kinesthetic illusions in absence of visual feedback [1, 2]. This method strongly stimulates muscle spindles of the vibrated muscle, therefore sending proprioceptive information perceived by the person as an illusory feeling of movement coherent with the stretching of the stimulated muscle [3, 4]. Vibration-induced kinesthetic illusion has been recently proposed as an innovative diagnostic and therapeutic approach for individuals with somatosensory and motor deficits [5-7], for instance, resulting from stroke, dystonia, multiples sclerosis or musculoskeletal injuries [8].

Mechanisms involved in the processing of vibration-induced afferents have been studied in the past with the use of different neurophysiological tools, including neuroimaging [9, 10] and transcranial magnetic stimulation of the primary motor cortex (TMS) [2, 11, 12]. Studies that used neuroimagery during VIB found a higher activation of motor cortical areas when VIB induced kinesthetic illusions [9, 10]. Pairing tendon vibration with TMS provides a unique way of probing sensorimotor transduction mechanisms within networks involved in motor programming and control [2, 13]. So far, most previous studies vibrated musculotendinous structures without inducing kinesthetic illusions (for example with eyes open and looking at the vibrated limb) and often found an increase in corticospinal excitability of the vibrated muscle [11, 12, 14], an effect that was sometimes sustained for at least 30 minutes [15, 16]. For the few studies that elicited illusions, there is still a misunderstanding of the mechanisms behind these sensations. However, evidence tends to show an increase in the antagonist muscle activity [1, 10], i.e. those that would be involved in controlling the perceived movement. Although

evidence about the impact of VIB on neural networks remains scarce, it does underscore that vibration-induced afferents interact with motor cortex and corticospinal networks. However, most previous studies tested the after-effects of a repeated VIB application on corticomotor excitability [15, 17, 18]. Therefore, the time course of corticospinal excitability tested *during* the perception of a kinesthetic illusion has not been extensively studied and could provide important knowledge on time-specific mechanisms of sensorimotor processing occurring during the illusion. Some studies have demonstrated that kinesthetic illusion takes a certain time to build-up during VIB [19] and that stronger perceptions tend to be associated with more activity in sensorimotor control networks [20, 21]. However, there are conflicting results in the literature regarding the effects of VIB on TMS measurements. There are studies having reported an increased, unchanged or lower corticospinal excitability for vibrated [2, 22] and non-vibrated muscles [17, 21, 23]. Such heterogeneity might be related to the different timings of TMS delivery that were so far arbitrarily applied (e.g. 1 sec after VIB start for [12], 3 sec for [23] and 4 sec for [2]). Overall, most studies found that corticospinal excitability tends to increase in vibrated muscle, or in some cases in unvibrated muscle. More studies are needed to better understand the time-specific modulation of corticospinal excitability during VIB-induced illusions.

The main objective of this study was to investigate corticospinal excitability at different time points (1s, 5s, 10s) during vibration-induced kinesthetic illusions. We hypothesized that a progressive build-up of corticospinal excitability is observed during the first 5s in antagonist muscles since illusions are typically increasing in strength/speed and probability of occurence in the first few seconds [3, 19, 22]. Similar or lower corticospinal excitability are expected at 10s

compared to 5s, considering that illusions are most often either continuing at constant speed or slowing down/disappearing when high joint amplitudes are reached [3, 19].

Materials and Methods

Participants: Twenty healthy participants were recruited for one experimental session of about 1.5 hours realized at the BioNR research laboratory (*Université du Québec à Chicoutimi*). Selection criteria were to be aged between 18 and 35 years old and have no neurological or musculoskeletal disorders affecting the upper limb. Participant's characteristics are detailed in *Table 1*. Ethical approbation (#2020-409) was obtained before recruitment and all participants gave their written consent before the beginning of the experiment.

Experimental procedure: Participants first completed 3 questionnaires: (i) a questionnaire about personal characteristics (i.e. age, sex, height, weight, comorbidity, medical background), [24] the Global Physical Activity Questionnaire (QPAQ) [25] and (iii) the Edinburgh Handedness Inventory short form (EHI) [26]. A screening was then proceeded by the same evaluator for both wrists to ensure that participants had a normal somatosensory function, using the following validated tests: (i) Semmes-Weinstein monofilaments (hand set) to assess sensitivity to pressure [24]; [24] 128 Hz tuning fork to assess vibratory sensation [27] and (iii) Nottingham Sensory Assessment to test wrist proprioception [28]. Participants were seated in a chair with their arm supported on a table and their vision was obstructed during the whole experiment (Figure 1). All procedures were repeated on the dominant and non-dominant sides for each participant in a randomized order.

Insert Table 1 and Figure 1 near here

Vibration procedure: Kinesthetic illusions were induced by a custom-made vibratory device which consist of a vibration motor (Precision Microdrives, London, UK) and controlled via MATLAB software (Mathworks, Natick, Massachussetts, USA). Vibration was applied over the forearm on the wrist flexor tendons (80 Hz frequency, ~1mm amplitude, 10 seconds)[29] with the intention of inducing an illusion of wrist extension. Standardized Kinesthetic Illusions Procedure (SKIP) was strictly followed to standardize directives given to the participant to identify an optimal joint position and to qualitatively measure the perceived illusory movement (for more details [29]). The optimal joint position was individualized for each participant as the angular position eliciting the clearest perception of movement. To do so, different angles were tested by 5 degrees increments between 0 and 90 degrees of wrist extension, measured with a light plastic goniometer strapped on the subject's wrist (see Figure 1). The angle eliciting the best illusion was noted and strictly reproduced for all further VIB trials. The SKIP rating sheet was used to qualify illusions in terms of clearness/precision (perfectly clear and precise = 3; moderately clear/precise = 2; vague and not precise = 1; no illusion = 0) and direction (illusion in the expected direction (i.e. which would stretch the vibrated tendons) = 1; any other direction = 0).

TMS procedures: Surface electromyography followed SENIAM recommendations for electrodes' placement and standard skin preparation [30]. Ag-AgCl electrodes (Kendall, Cardinal Health

149 Canada Inc, Ontario, Canada) were placed 1 cm apart on the belly of extensor digitorium
150 communis (EDC) muscle on both dominant and non-dominant sides. The ground electrode was
151 placed over the olecranon on the tested side. Electromyographic signals were amplified (x1000)
152 before digitization at 2 kHz sampling rate (1902 & 1401 systems, Cambridge Electronic Design
153 Limited, UK) and computer-stored for online display and offline analysis (Spike 2 software,
154 Cambridge Electronic Design Limited, UK). Single-pulse (monophasic, 400μs pulse width,
155 posteroanterior electric current direction in the cortex) TMS was delivered using a MagStim
156 200^2 (MagStim Company, UK) through a 70 mm diameter figure-of-eight coil placed tangentially
157 to the scalp with the handle oriented 45° in the mid-sagittal plane [31]. The vertex and primary
158 motor cortex (M1) were first identified using the 10-20 EEG system [32]. Then, the location and
159 coil position eliciting the largest motor evoked potentials (MEP) at lowest stimulus intensity in
160 the contralateral EDC muscle (i.e. the hotspot) was identified and marked on the scalp using a
161 surgical pen to ensure reliable positioning and orientation of the coil throughout the testing
162 session [31]. EMG was constantly monitored during TMS measurements to visually ensure
163 complete relaxation of the tested muscle. EMG recordings for analysis include an interval of 50
164 ms before and 5000 ms after TMS stimulation. Resting motor threshold (rMT) was found using
165 the Motor Threshold Assessment Tool 2.0 software (MTAT 2.0) (Clinicalresearcher.org, South
166 Carolina, USA) which estimates the lowest stimulation intensity to evoke motor evoked
167 potential (MEP) greater than 50 μV based on a threshold-hunting algorithm [13, 33]. The rMT
168 identification procedure was stopped when its estimation reached a 95% confidence level,
169 which often required 30-40 trials at various intensities. TMS was delivered at 120% rMT in four
170 conditions (10 trials/condition, random order of conditions between participants and sides)

consisting of different timings between vibration start and TMS delivery: baseline condition without vibration (Baseline), TMS delivered 1s (t1), 5s (t5) and 10s (t10) after vibration start. TMS was automatically trigged by vibration start using a synchronisation circuit linked to the control interface of the vibration system developed by our team on Matlab.

Data reduction and statistical analysis: Two TMS outcome measures were acquired: (i) mean from 10 trials for MEP latency (onset of TMS artifact to onset of MEP) reflecting brain-muscle conduction time and (ii) peak-to-peak MEP amplitude reflecting the volume of M1 cells activated by TMS and temporal summation/synchronization of descending volleys within the corticospinal track [13]. However, only MEP latency and amplitude were collected during the four experimental conditions testing how vibration influences corticospinal excitability. No MEP was excluded from the statistical analysis (if there was no MEP after a particular trial even though the experimental setup was correct, "0 mV" amplitude was entered in the data). Statistical analysis was complete with SPSS version 26 (Armonk, NY, United States) with a significant alpha risk below 0.05. Data normality and the absence of outliers were respectively confirmed by the Shapiro-Wilk test and visual screening of box-and-whiskers produced by SPSS in which outliers are automatically identified. Of note, sphericity assumption was sometimes violated but appropriately corrected using the Greenhouse-Geiser method. Data from dominant and non-dominant sides were pooled to explore the global effect of stimulation timings with an increased statistical power. A within-subject analysis of variance (ANOVA) was applied using factors *Stimulation timings* (Baseline, t1, t5 and t10) and *side* (dominant and non-dominant). In cases of significant effects in ANOVA results, pair-wise Bonferroni tests were realized between

timing conditions. The effect sizes (Cohen's D_z ES) were calculated (based on formulas proposed by [34]) whenever relavant to give a perspective about the magnitude of the effects (large if >0.8, moderate if >0.5, small if >0.2 and null if <0.2) (Supplemental table 1).

Results

Kinesthethic illusion perceptions were stable across each VIB conditions according to SKIP scores (Table 2), demonstrating mostly moderately a clear and precise illusion in the expected direction. After careful post-hoc examination of EMG traces from 50ms before to 5000ms after each TMS delivery, we found no evidence of EMG activity, therefore confirming that the target muscle remained at rest throughout the experiment. EMG mean noise level was low (61.50 ± 35.28 μV) across all trials and was mainly caused by the noise of the VIB device. Furthermore, as included in the SKIP scoring form, the evaluator never detected, while keeping their focus on the hand and wrist of the participant, any vibratory-induced motor contractions such as antagonist vibratory responses (AVR) or tonic vibratory responses (TVR). Of note, TVR can be elicited in the vibrated muscle in the absence of a kinesthetic illusion and is related to spinal reflex loops whereas the AVR is observed in muscles antagonists to the vibration in the presence of kinesthetic illusion and involves higher-order sensorimotor transduction mechanisms [1, 3, 35]. These phenomena are not systemically observed when applying VIB, as reported in the present work and others [1, 22].

Effect of VIB on corticospinal excitability : Within-subject ANOVA found no interaction between timings and side, and no main effects of side were found. A large effect of timings on MEP

amplitudes was detected [F=3.797 (1.86; 35.27), p=0.035, η_p^2 = 0.167)]. Of note, Mauchly's Test of Sphericity indicated that the assumption of sphericity had been violated [$\chi 2(5) = 19.619$, *p* =0.002]. The Greenhouse-Geisser correction was applied to correct the degrees of freedom and significance value. As shown in fig 2.A, pair-wise comparisons showed that MEP amplitudes were significatively lower in t1 compared to t5 (p=0.025) and t10 (p=0.003) with moderate effect sizes (Cohen's D_z respectively at 0.523 and 0.635) (Supplemental table 1). For exploratory purposes, an independent analysis of each side was performed. When each hemisphere was analyzed independently, ANOVA did not show a significant difference between stimulation timings (figure 2.B). No difference was found between baseline and t1-t5-10 data. No effect of timing was found for MEP latency measures.

Insert Table 2, Table 3 and Figure 2 near here

Discussion

The present study investigated the modulating influence of vibration-induced proprioceptive inflow and kinesthetic illusion on corticospinal excitability. Our results only partially support the initial hypothesis. As anticipated, MEP amplitudes at 5s and 10s after vibration onset were statistically higher compared to those obtained at 1s, with no further significant increase between 5s and 10s time-points. However, no statistical difference between baseline measures was found, and the overall portrait (Figure 2) suggests that corticospinal excitability might in fact decrease early after vibration start, and then re-stabilizes near baseline values toward mid and end time-points of the 10-s vibration period. The potential neurophysiological

underpinnings of these observations along with their recommendations for future applications of VIB-induced illusions are discussed below.

Effect of VIB on corticospinal excitability

Only a few studies tested the effects of VIB-induced illusions on corticospinal excitability in healthy population. Mancheva et al. [2] applied VIB in 15 participants over wrist flexors using three experimental conditions. The control condition (eyes open and looking at the vibrated hand) had no effect on corticospinal excitability, whereas the two conditions of illusion (eyes closed & eyes open but hand hidden from sight) led to a significant increase in MEP amplitudes for the vibrated flexor muscles. The illusion condition with eyes open also caused a significant increase in MEP amplitudes for wrist extensors. Naito et al. 2002 [21] applied VIB over wrist extensors in eight participants while the hand of the vibrated side laid over the dorsal part of the non-vibrated hand. Participants reported perceiving both of their hands flexing, and corticospinal excitability was influenced only in conditions where a kinesthetic illusion was present, like Mancheva et al.'s observations. However, corticospinal changes were not in the same direction: they were respectively upregulated (higher MEP amplitudes and lower latencies) for the antagonistic muscles (wrist flexors) and downregulated for the vibrated ones (extensors). Talis et al. [22] also elicited illusions of wrist movement by vibrating wrist flexors and extensors and applied TMS during VIB. However, the comparison between their results and other studies, including ours, is hindered by important methodological differences (i.e. TMS triggered by the occurrence of EMG activity in the tested muscles, TMS outputs measured in terms of a 'muscle response' instead of a MEP, i.e. min-max EMG over the 10–100 msec period

after TMS). They did however observe increases in TMS-evoked muscle responses during VIB, especially when vibrating wrist extensors. The literature having verified the influence of kinesthetic illusions on corticospinal excitability remains scarce, heterogeneous and controversial. Nevertheless, they underscore the relevance of VIB-induced illusions for unveiling and studying the role of the primary motor cortex in movement perceptions [21, 36].

Other studies tested the effects of VIB on corticospinal excitability, but without creating kinesthetic illusions. Using a short VIB duration of 1.5s, Rosenkranz et al. observed higher MEP amplitudes for the vibrated intrinsic hand muscles and the opposite effect (reduction of MEP amplitudes) for the non vibrated muscles at 1s after VIB onset [12]. The same pattern was found by other authors, i.e. an increased MEP amplitudes and shortening of MEP latencies at 3s after VIB start for the vibrated wrist extensors [37] or wrist flexors [38] and the opposite effect observed in the non vibrated antagonist muscle [38]. Paired-pulse TMS paradigms, used to indirectly estimate the integrity of mechanisms of intracortical inhibition and facilitation in the motor cortex [13], have shown a reduction of cortical inhibition (= disinhibition) for the vibrated muscle [12, 38] and an increased inhibition for the antagonist [38]. Of note, all these studies only delivered TMS at one time during VIB, all below 5 s. There are other studies that, which like us, stimulated at different time points during VIB (but without eliciting an illusion) to investigate the time course of corticospinal excitability. Siggelkow et al. vibrated wrist extensor muscles for 4s and delivered TMS at 0.5s and 3s after VIB start. MEP amplitudes were significantly depressed compared to a control condition without VIB for the antagonist wrist flexors, particularly at 0.5s compared to 3s (similarly to what we found at 1s vs. 5s time points) and with the opposite pattern observed for the vibrated wrist extensor muscles [11]. In another study,

VIB was applied for 60s over the Achilles' tendon and mean TMS measures were obtained with the 3 maximal responses out of 10 random timings during VIB (first at 3s after VIB onset and others were taken with inter-stimulation timings varying from 3s to 10s). Their results did not show any effect on the non vibrated antagonistic muscle, but an increased excitability was present for the vibrated one [14].

Overall, evidence from the literature underscores the key influence of perceiving or not a kinesthetic illusion. As described above, opposite effects are often reported between the vibrated and antagonistic muscles [11, 12, 38], but the direction of these effects is not always similar between studies. It seems that VIB has mostly an excitatory influence on M1 and corticospinal networks [36], but the resulting effect depends on how the nervous system process the induced proprioceptive afferents. In the absence of an illusion, the effect tends toward an increased corticospinal drive for the control of vibrated muscles [11, 12, 14, 37-40]. This could be linked for instance to a counteractive response to an unanticipated stretching of the muscle in order to maintain stability/posture of the disturbed joint position [41]. Conversely, perceiving a kinesthetic illusion would favor an increased excitability in networks involved in the sensorimotor control of this movement, hence favoring an increase in corticospinal excitability of antagonistic muscles to the vibration [2, 21, 36]. In support of the hypothesis that different mechanisms and networks are involved in the presence vs. absence of illusions, Romaiguere et al. studied the impact of kinesthetic illusion with functional neuroimagery and found that motor and parietal cortex were activated during VIB-induced illusions whereas these regions were little or not activated in the absence of an illusion [9].

In our study, we stimulated wrist flexors to induce a kinesthetic illusion of extension and tested corticospinal excitability of the antagonist muscles. Our results do not add further evidence of an excitatory influence of kinesthetic illusion on agonistic muscles to the vibration since MEP amplitudes at t1, t5 and t10 did not reach statistical significance compared to baseline data without VIB. However, we found a significant variation of corticospinal excitability during VIB that showed a contrasting effect between the early (1s) versus mid (5s) and late (10s) periods. When looking at Figure 2, our data mostly suggest a first decrease of MEP amplitude 1s after VIB start. Three previous studies already found a similar decrease of MEP amplitudes early after VIB start, particularly evident at 0.5s [11, 12, 38]. This early pattern of reduced corticospinal excitability toward antagonistic muscles could be explained by the fact that kinesthetic illusions take time to build in clearness and speed [22]. Therefore, an increase in corticospinal drive might first occur in vibrated muscles with the opposite effect for antagonistic muscles, as shown in previous studies [11, 12, 38]. Our results then suggest a return to baseline level of corticospinal excitability at 5s and 10s during VIB, which could be linked to a change in underlying mechanisms when the illusory perception emerges. The specific mechanisms involved can only be speculated since the respective contribution of spinal and cortical networks cannot be distangled from TMS-related measures of MEP amplitudes. Still, it can be argued that early changes in corticospinal excitability between antagonistic muscles could involve spinal mechanisms of reciprocal inhibition [37, 38]. Then, when clear illusions are perceived after a few seconds, a shift in excitability changes between the vibrated muscles and their antagonists,potentially related to the removal of reciprocal inhibition and/or increase in corticospinal drive toward antagonistic muscles [9, 20]. To test this hypothesis, it would be

important to precisely track the emergence and evolution of kinesthetic perceptions, so that any neurophysiological effects can be correlated to perceptual changes. This could be realized using a potentiometer or manipandulum connected to a computer and strapped on the untested wrist so that the participant can mimick the sensory perceptions in real time [42].

Study limitations and future considerations:

Lacking concomitant neurophysiological measures of spinal networks, as well as scarce and controversial evidence from the literature preclude from proposing reliable explanations about mechanisms underlying our results. Results from our study and others [12, 14] encourage to further investigate spinal (i.e using electrical nerve stimulation and H/M and F waves paradigms for testing spinal and motoneuronal circuitries [16, 37]), cortical (brain imagery [9, 20, 43]) and corticospinal (TMS [18, 38]) mechanisms involved in processing VIB-induced afferents. It would be highly interesting to precisely track the timecourse of kinesthetic perceptions to verify if their apparition/absence/disappearance coincide with shifting of excitability between the vibrated and antagonistic muscles. This could maybe help reconcile some of the controversial results in the literature, considering that TMS timing delivery is so far mostly arbitrarily determined and varies between studies. Completely opposite corticospinal effects (with likely different underlying mechanisms) could be obtained depending on the chosen time of TMS testing, hence adding an important factor of variation that remains so far overlooked. Since we did not include a control condition of vibration, such as vibrating over a nearby bony structure, we cannot rule out the potential contribution of a generalized effect of VIB rather than specific to kinesthetic perceptions. Although previous studies mostly support

that neurophysiological effects of VIB depend on the absence/presence of an illusion [11, 14, 21, 22], adding such a control condition would have added relevant data for interpreting our results. To ensure the specific effects of our results, it would have been interesting to add a control measure such as recording the activity of another nearby muscle or another control condition without inducing illusion (i.e. by applying VIB over a bone or at very low intensity). Another factor that should be considered while interpreting our results is the unknown stability of rMT throughout TMS testing and VIB application. Some authors suggest that rMT could be decreased after VIB application [7, 16] while other demonstrated that rMT did not significantly change at rest versus during VIB [38]. rMT has been proposed as a stable and reliable TMS variable that is less suited to track rapid changes of corticospinal excitability compared to MEP amplitude [44]. Since rMT was not verified at the end of the protocol, it remains uncertain if changes of MEP amplitudes are linked to a potential change of rMT. The sample size is small and results can only be generalized to healthy and young individuals, therefore limiting the clinical usefulness of our findings. Nevertheless, our results suggest a strong effect of timing with moderate effects observed for significant paired comparisons despite the small sample studied. The effect of manual dominance could have been a confounding factor in the interpretation of the results. Only a few studies investigated interhemispheric differences of proprioceptive coding and corticospinal excitability, but none used a combined paradigm of vibration and TMS. They mostly found interhemispheric differences in the lateralization of sensorimotor function. Indeed, the right hemisphere appeared to have a dominant role in the processing and perception of a kinesthetic illusion [20, 43]. In our study, no effect of side was found for both VIB and TMS measures. Further research is required to determine if kinesthetic illusions are

processed differently by the motor cortex according to handedness and hemispheric lateralization of proprioceptive coding. Also, we arbitrarily selected the timepoints of TMS measures and VIB duration. Including more TMS measures at several time-points that can be linked to predictable phases of VIB processing (i.e. before afferents reach the cortex, before illusion is perceived, at highest illusion strength, when the illusion disappears, etc.) would bring better insights on neurophysiological underpinnings of VIB-induced proprioceptive coding.

Conclusion

To conclude, our results suggest that there is a dynamic modulation of corticospinal excitability during kinesthetic illusions, that which mostly tend toward a lower excitability of muscles antagonistic to the vibration during the early period after VIB start compared to later phases where the illusory perceptions are likely stronger. Whether this modulation of excitability actually depends on the time-specific emergence of a clearly perceptible illusion remains to be validated in the future. Results from previous studies have demonstrated promising effects of VIB on motor function and neural plasticity in corticospinal networks [17, 36, 45], however, the underlying explanatory mechanisms remain poorly understood. A better understanding of these mechanisms is needed before considering this modality in the clinical management of proprioceptive disorders.

References

1. Calvin-Figuiere, S., et al., *Antagonist motor responses correlate with kinesthetic illusions induced by tendon vibration.* Exp Brain Res, 1999. **124**(3): p. 342-50.
2. Mancheva, K., et al., *Vibration-Induced Kinesthetic Illusions and Corticospinal Excitability Changes.* J Mot Behav, 2017. **49**(3): p. 299-305.

3. Roll, J.P. and J.P. Vedel, *Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography.* Exp Brain Res, 1982. **47**(2): p. 177-90.
4. Roll, J.P., J.P. Vedel, and E. Ribot, *Alteration of proprioceptive messages induced by tendon vibration in man: a microneurographic study.* Exp Brain Res, 1989. **76**(1): p. 213-22.
5. Conrad, M.O., R.A. Scheidt, and B.D. Schmit, *Effects of wrist tendon vibration on arm tracking in people poststroke.* J Neurophysiol, 2011. **106**(3): p. 1480-8.
6. Poenaru, D., et al., *Local Application of Vibration in Motor Rehabilitation - Scientific and Practical Considerations.* Maedica (Bucur), 2016. **11**(3): p. 227-231.
7. Souron, R., et al., *Acute and chronic neuromuscular adaptations to local vibration training.* Eur J Appl Physiol, 2017. **117**(10): p. 1939-1964.
8. Aman, J.E., et al., *The effectiveness of proprioceptive training for improving motor function: a systematic review.* Front Hum Neurosci, 2014. **8**: p. 1075.
9. Romaiguere, P., et al., *Motor and parietal cortical areas both underlie kinaesthesia.* Brain Res Cogn Brain Res, 2003. **16**(1): p. 74-82.
10. Naito, E., et al., *Human limb-specific and non-limb-specific brain representations during kinesthetic illusory movements of the upper and lower extremities.* Eur J Neurosci, 2007. **25**(11): p. 3476-87.
11. Siggelkow, S., et al., *Modulation of motor evoked potentials by muscle vibration: the role of vibration frequency.* Muscle Nerve, 1999. **22**(11): p. 1544-8.
12. Rosenkranz, K. and J.C. Rothwell, *Differential effect of muscle vibration on intracortical inhibitory circuits in humans.* J Physiol, 2003. **551**(Pt 2): p. 649-60.
13. Rossini, P.M., et al., *Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee.* Clin Neurophysiol, 2015. **126**(6): p. 1071-1107.
14. Lapole, T., et al., *Achilles tendon vibration-induced changes in plantar flexor corticospinal excitability.* Exp Brain Res, 2015. **233**(2): p. 441-8.
15. Bisio, A., et al., *Kinaesthetic illusion shapes the cortical plasticity evoked by action observation.* J Physiol, 2019. **597**(12): p. 3233-3245.
16. Christova, M., et al., *Vibration stimulation during non-fatiguing tonic contraction induces outlasting neuroplastic effects.* J Electromyogr Kinesiol, 2010. **20**(4): p. 627-35.
17. Marconi, B., et al., *Long-term effects on cortical excitability and motor recovery induced by repeated muscle vibration in chronic stroke patients.* Neurorehabil Neural Repair, 2011. **25**(1): p. 48-60.
18. Lapole, T., et al., *Acute effects of Achilles tendon vibration on soleus and tibialis anterior spinal and cortical excitability.* Appl Physiol Nutr Metab, 2012. **37**(4): p. 657-63.
19. Seizova-Cajic, T., et al., *Proprioceptive movement illusions due to prolonged stimulation: reversals and aftereffects.* PloS one, 2007. **2**(10): p. e1037.
20. Naito, E., T. Morita, and K. Amemiya, *Body representations in the human brain revealed by kinesthetic illusions and their essential contributions to motor control and corporeal awareness.* Neurosci Res, 2016. **104**: p. 16-30.
21. Naito, E., P.E. Roland, and H.H. Ehrsson, *I feel my hand moving: a new role of the primary motor cortex in somatic perception of limb movement.* Neuron, 2002. **36**(5): p. 979-88.

22. Talis, V.L., I.A. Solopova, and O.V. Kazennikov, *Changes in corticospinal excitability in the reactions of forearm muscles in humans to vibration.* Neurosci Behav Physiol, 2010. **40**(1): p. 21-8.
23. Rosenkranz, K., et al., *Alteration of sensorimotor integration in musician's cramp: impaired focusing of proprioception.* Clin Neurophysiol, 2000. **111**(11): p. 2040-5.
24. Suda, M., et al., *Validity and Reliability of the Semmes-Weinstein Monofilament Test and the Thumb Localizing Test in Patients With Stroke.* Front Neurol, 2020. **11**: p. 625917.
25. Bull, F.C., T.S. Maslin, and T. Armstrong, *Global physical activity questionnaire (GPAQ): nine country reliability and validity study.* J Phys Act Health, 2009. **6**(6): p. 790-804.
26. Veale, J.F., *Edinburgh Handedness Inventory - Short Form: a revised version based on confirmatory factor analysis.* Laterality, 2014. **19**(2): p. 164-77.
27. Prabhakar, A.T., et al., *Timed Vibration Sense and Joint Position Sense Testing in the Diagnosis of Distal Sensory Polyneuropathy.* J Neurosci Rural Pract, 2019. **10**(2): p. 273-277.
28. Lincoln, N.B., J.M. Jackson, and S.A. Adams, *Reliability and Revision of the Nottingham Sensory Assessment for Stroke Patients.* Physiotherapy, 1998. **84**(8): p. 358-365.
29. Beaulieu, L.D., et al., *A new method to elicit and measure movement illusions in stroke by means of muscle tendon vibration: the Standardized Kinesthetic Illusion Procedure (SKIP).* Somatosens Mot Res, 2020. **37**(1): p. 28-36.
30. Hermens, H.J., et al., *Development of recommendations for SEMG sensors and sensor placement procedures.* Journal of Electromyography and Kinesiology, 2000. **10**(5): p. 361-374.
31. Groppa, S., et al., *A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee.* Clin Neurophysiol, 2012. **123**(5): p. 858-82.
32. Klem, G.H., et al., *The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology.* Electroencephalogry and Clinical Neurophysiology, 1999. **52**(3): p. 3-6.
33. Awiszus, F. and J. Borckardt, *TMS Motor Threshold Assessment Tool (MTAT 2.0).* 2010.
34. Lakens, D., *Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs.* Front Psychol, 2013. **4**: p. 863.
35. Eklund, G. and K.E. Hagbarth, *Normal variability of tonic vibration reflexes in man.* Exp Neurol, 1966. **16**(1): p. 80-92.
36. Dilena, A., et al., *What is the effect of bodily illusions on corticomotoneuronal excitability? A systematic review.* PLoS One, 2019. **14**(8): p. e0219754.
37. Kossev, A., et al., *Muscle vibration: different effects on transcranial magnetic and electrical stimulation.* Muscle Nerve, 1999. **22**(7): p. 946-8.
38. Rosenkranz, K., et al., *Focal reduction of intracortical inhibition in the motor cortex by selective proprioceptive stimulation.* Exp Brain Res, 2003. **149**(1): p. 9-16.
39. Liepert, J. and C. Binder, *Vibration-induced effects in stroke patients with spastic hemiparesis--a pilot study.* Restor Neurol Neurosci, 2010. **28**(6): p. 729-35.
40. Schrader, C., et al., *Changes in processing of proprioceptive information in Parkinson's disease and multiple system atrophy.* Clin Neurophysiol, 2008. **119**(5): p. 1139-46.
41. Diener, H.C., et al., *Variability of postural "reflexes" in humans.* Exp Brain Res, 1983. **52**(3): p. 423-8.

42. Conrad, M.O., et al., *Effect of Tendon Vibration on Hemiparetic Arm Stability in Unstable Workspaces.* PLoS One, 2015. **10**(12): p. e0144377.
43. Naito, E., et al., *Development of Right-hemispheric Dominance of Inferior Parietal Lobule in Proprioceptive Illusion Task.* Cereb Cortex, 2017. **27**(11): p. 5385-5397.
44. Beaulieu, L.D. and M.H. Milot, *Changes in transcranial magnetic stimulation outcome measures in response to upper-limb physical training in stroke: A systematic review of randomized controlled trials.* Ann Phys Rehabil Med, 2018. **61**(4): p. 224-234.
45. Beaulieu, L.D., et al., *After-effects of peripheral neurostimulation on brain plasticity and ankle function in chronic stroke: The role of afferents recruited.* Neurophysiol Clin, 2017. **47**(4): p. 275-291.