

Plastic changes induced by muscle focal vibration: a possible mechanism for long-term motor improvements

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GMF, AR, LF and VEP conceived the outline of the review. These authors contributed equally to this work and share first authorship. MF and GR supervised project and provided suggestions to the manuscript revisions. All authors have read and approved the final version of the manuscript and agree with the order of the presentation of the authors.

Keywords

long term potentiation, physical exercise, Rehabilitation, Proprioception, Motor Cortex

Abstract

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Repetitive focal vibrations can induce positive and persistent after-effects. There is still no satisfactory interpretation of the underlying mechanisms. A rationale, which can provide consistency among different results, is highly desirable to guide both the use of the application and future research. To date, interpretive models are formulated to justify the results, depending on the specific protocol adopted. Indeed, protocol parameters, such as stimulus intensity and frequency, intervention time and administration period, are variable among different studies. However, in this article, we have identified features of the protocols that may allow us to suggest a possible common mechanism underlying the effectiveness of focal vibration under different physiologic and pathologic conditions. Since repetitive focal muscle vibration induces powerful and prolonged activation of muscle proprioceptors, we hypothesize that this intense activation generates adaptive synaptic changes along sensory and motor circuits. This may lead to long-term synaptic potentiation in the central network, inducing an enhancement of the learning capability. The plastic event could increase proprioceptive discriminative ability and accuracy of the spatial reference frame and, consequently, improve motor planning and execution for different motor functions and in the presence of different motor dysfunctions. The proposed mechanism may explain the surprising and sometimes particularly rapid improvements in motor execution in healthy and diseased individuals, regardless of specific physical training. This hypothetic mechanism may require experimental evidence and could lead to extend and adapt the application of the "learning without training" paradigms to other functional and recovery needs.

Contribution to the field

Dear Editor, We would like to ask you permission to submit on the Frontiers in Neuroscience a perspective work aimed to describe possible neurophysiological changes induced by focal vibration (FV). In literature, a large amount of works have adopted interventions with FV on healthy and diseased subjects, but the neural mechanisms involved are not clearly defined. In those works, protocols and stimulus characteristics are largely variable as well as the motor performance tested. All of this makes the physiological results explanation very complex and valid case by case. In spite, positive long-term FV effects on motor performances are largely described and a considerable amount of works have proposed the FV administration in the clinic and rehabilitation fields, other than in athletes. Present work aims to describe possible neural modification and mechanisms to explain FV after-effects and tries to define eventual differences among the different FV intervention protocols. Our proposals have obtained by means of a comparative literature analysis to address the performance after-effects without others form of motor conditioning. Work highlights neural pathways and areas, and their changes, involved with the administration of sole FV in order to explain both the positive changes in motor performances and, especially, their long-term duration. Finally, is in our minds the idea that a deep knowledge of physiological mechanisms could be useful to define new fields of study in the area of neural and motor rehabilitation. The components of our group show different scientific skills in muscle focal vibration as stressor as well as a form of motor function booster, both for theoretical and occupational scope, in healthy and diseased individuals.

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In review

1 **Plastic changes induced by muscle focal vibration: a possible mechanism for long-**
2 **term motor improvements.**

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16 **Cortex**

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20 **Abstract**

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22 interpretation of the underlying mechanisms. A rationale, which can provide consistency among
23 different results, is highly desirable to guide both the use of the application and future research. To
24 date, interpretive models are formulated to justify the results, depending on the specific protocol
25 adopted. Indeed, protocol parameters, such as stimulus intensity and frequency, intervention time and
26 administration period, are variable among different studies. However, in this article, we have identified
27 features of the protocols that may allow us to suggest a possible common mechanism underlying the
28 effectiveness of focal vibration under different physiologic and pathologic conditions. Since repetitive
29 focal muscle vibration induces powerful and prolonged activation of muscle proprioceptors, we

30 hypothesize that this intense activation generates adaptive synaptic changes along sensory and motor
31 circuits. This may lead to long-term synaptic potentiation in the central network, inducing an
32 enhancement of the learning capability. The plastic event could increase proprioceptive discriminative
33 ability and accuracy of the spatial reference frame and, consequently, improve motor planning and
34 execution for different motor functions and in the presence of different motor dysfunctions. The
35 proposed mechanism may explain the surprising and sometimes particularly rapid improvements in
36 motor execution in healthy and diseased individuals, regardless of specific physical training. This
37 hypothetic mechanism may require experimental evidence and could lead to extend and adapt the
38 application of the "learning without training" paradigms to other functional and recovery needs.

39

40 **Introduction**

41 Specific, intensive, long-term physical training is usually required to achieve improvements in
42 motor performance or motor recovery after functional impairment. An ambitious goal is to minimize
43 the required training period or to ameliorate outcomes with non-invasive complementary approaches.
44 Proprioceptive training has been shown to be frequently proposed (Aman et al., 2015) as a feasible
45 procedure to improve motor function, due to the crucial role of proprioceptive signals in motor control
46 (Wiesendanger and Miles, 1982). To ameliorate motor performance, several authors stimulated
47 proprioceptive sensors by applying a prolonged and repeated mechanical vibration on a muscle or
48 tendon (RFV, repeated focal vibration). RFV has been found to induce, in most cases, long-term (days,
49 weeks, or months) improvements of motor performances in both healthy and diseased individuals
50 (Murillo et al., 2014; Souron et al., 2017a; Alghadir et al., 2018; Fattorini et al., 2021). Even though
51 the results were mainly related to the function of the single treated muscle, RFV has been found to
52 induce complex, unexpected, and still unexplained motor effects also involving untreated muscles.
53 Moreover, RFV ameliorates motor performance in diseased individuals even in the presence of
54 opposite motor disabilities, such as muscle weakness and paresis or spasticity on the other (Karnath,
55 1994; Kerkhoff, 2003; Brunetti et al., 2006, 2012, 2015; Filippi et al., 2009; Pietrangelo et al., 2009;
56 Camerota et al., 2011, 2016, 2017; Celletti et al., 2011, 2015, 2017a; Marconi et al., 2011; Caliandro
57 et al., 2012; Pettorossi and Schieppati, 2014; Pettorossi et al. 2015; Rabini et al., 2015; Pazzaglia et
58 al., 2016; Attanasio et al., 2018; Russo et al. 2019).

59 Therefore, to provide a possible justification for the focal vibration effectiveness in such variety
60 of effects it is necessary to propose a common mechanism of action in normal and dysfunctional

61 conditions. The basic idea of this proposed mechanism is that a repeated high frequency mechanical
62 stimulation may facilitate synaptic plasticity along the proprioceptive pathway and in central motor
63 area. These changes should be able to increase the responsiveness of the network and its adaptive
64 abilities (Marconi et al., 2008, 2011; Rocchi et al., 2018). This is in analogy with what has already
65 been observed in other sensory systems, where nonspecific stimulation of other sensory system has
66 been shown to induce specific and selective learning, enhancing sensory discrimination and motor
67 learning (Pleger et al., 2003; Frenkel et al., 2006).

68

69 **New idea for learning along the proprioceptive system**

70 Sensory stimulation, such as repetition of tactile, visual or auditory stimuli, has been shown to
71 improve perceptual resolution (Pleger et al., 2003; Frenkel et al., 2006; Clapp et al., 2012; Beste and
72 Dinse, 2013), persisting over time. This after-effect was attribute to a specific mechanism termed
73 “learning without training“, a “learning induced in simple or complex motor or sensory performance
74 without specific training, with the aim of changing perception and behaviour” (cit. Beste and Dinse,
75 2013). These authors suggest that these effects, elicited by repetitive sensory stimulation, are likely
76 due to the induction of synaptic modification, like Long-term Potentiation (LTP) and Long-term
77 Depression (LTD) mechanisms, along the afferent pathways and in the primary and secondary
78 somatosensory areas. Specifically, with regard to the tactile system, it has been shown that the spatial
79 discrimination threshold is lowered by high-frequency tactile stimulation and it returns to control after
80 low frequency stimulation (Ragert et al., 2008). These behavioural results resembled those induced by
81 high frequency-LTP and low frequency-LTD *in vitro* (Bliss and Lomo, 1973; Stanton and
82 Sejnowski,1989; Bliss and Collingridge, 1993; Abraham and Williams, 2003). Furthermore, an
83 important role of N-methyl-D-aspartate (NMDA) receptors in this synaptic plasticity has been
84 demonstrated in human behavioural studies using memantine, a substance that selectively blocks the
85 NMDA receptors (Dinse et al., 2003). A single dose of memantine was found to suppress learning,
86 both behaviourally and in cortical circuits, providing evidence for the involvement of NMDA receptors
87 in training-independent sensory learning.

88 In analogy with these findings, we suggest that the high frequency, long-lasting proprioceptive
89 stimulation may elicit learning in the proprioceptive pathway through a change in synaptic activity that
90 increases the input resolution and the learning capability. The proposed RFV-induced adaptive
91 mechanism could guide further researches to analyse central excitability changes and to define the best
92 practices to combine the RFV after-effects with traditional rehabilitation and reconditioning protocols.

93 To provide evidences for the suggested mechanism, we report the RFV after-effects, observed
94 in healthy and diseased individuals, are described in section 1. In the section 2, we highlight the
95 characteristics of vibratory stimulation that support the induction of plastic events underlined our
96 proposed mechanisms. Finally, in section 3 we report spinal and cortical nervous circuitry changes that
97 could justify long-lasting RFV after-effects.

98

99 **Section 1: Immediate and sustained complex motor improvements induced by RFV**

100 *1.1 In healthy individuals.*

101 Several studies have examined the effects of focal vibration on healthy individuals. In a recent
102 review (Fattorini et al., 2021) the focus was on the long-lasting after-effects of RFV, ranging from 24
103 hours to several months after the end of RFV, in healthy individuals. In most of the articles listed in
104 the review, only one muscle was stimulated. Only occasionally two or more muscles were stimulated
105 in the same experiment. These investigations reported improvements in strength (Pietrangelo et al.,
106 2009; Lapole, and Pérot 2010; Iodice et al., 2011, 2019; Souron et al., 2017b; Feltroni et al., 2018),
107 power (Pietrangelo et al., 2009), fatigue resistance (Fattorini et al., 2006; Casale et al., 2009; Aprile et
108 al., 2016; Feltroni et al., 2018), rate of force development (Fattorini et al., 2006). These effects were
109 detected at the first test after the end of RFV, as early as 24 hours (Filippi et al., 2009; Lapole, and
110 Pérot, 2010; Brunetti et al., 2012; Contemori et al., 2021), or <60 minutes (Iodice et al., 2011; Aprile
111 et al., 2016; Feltroni et al., 2018; Filippi et al., 2020; Contemori et al., 2021). The different authors
112 considered such short latency as an important expression of a direct RFV action on the nervous system.
113 Then, the effects continued with a persisting or increasing trend until the end follow up, lasting days
114 (Casale et al., 2009; Lapole, and Pérot, 2010; Iodice et al., 2011), weeks (Fattorini et al., 2006; Aprile
115 et al., 2016; Souron et al., 2017b; Feltroni et al., 2018; Filippi et al., 2020; Contemori et al., 2021),
116 months (Filippi et al., 2009; Pietrangelo et al., 2009; Brunetti et al., 2012). In some of these studies,
117 the same protocol in the same subject produced effects that commonly require different, specific
118 physical training protocols. For example, quadriceps vibration improved both peak power and fatigue
119 endurance (Filippi et al., 2020), or peak velocity and fatigue endurance (Fattorini et al., 2006; Aprile
120 et al., 2016; Filippi et al., 2020), or power and knee laxity (Brunetti et al., 2012).

121 In addition, much more complex and multi-joint motor functions have been analysed in other
122 studies. Body balance (Filippi et al., 2009; Brunetti et al., 2015), movement fluidity (Aprile et al.,
123 2016) and accuracy (Contemori et al., 2021), have been found to improve after RFV. Improvements in
124 body balance, particularly under closed-eye conditions, were obtained by stimulating the quadriceps
125 muscle by RFV (Filippi et al., 2009; Brunetti et al., 2015). All these effects cannot be the result of

126 simple re-modelling of restricted nervous circuits since balance involves a multi-modal muscular
127 activation on different body segments to manage the centre of body mass. Moreover, smoothness of a
128 multi-joint movement is a parameter that requires precise proprioception-mediated efferent-afferent
129 control for the coordination of multiple muscles in different body segments (Aprile et al., 2016;
130 Contemori et al., 2021). In conclusion all the above studies support the effectiveness of the RFV not
131 only in modulating the local motor responses in the territory of the vibrated muscle but also in
132 interfering with the central circuits controlling posture and movements.

133

134 *1.2 In diseased individuals.*

135 Studies are available on subjects with different motor impairments, caused by central neurological
136 diseases, peripheral neuropathies, aging, osteoarthritis, orthopaedic problems, consequences of
137 surgery. The same RFV protocol facilitated motor recovery both in the presence of negative signs of
138 motor deficit as well as in asthenia, weakness, paresis, poor body balance, etc. (Brunetti et al., 2006,
139 2012, 2015; Filippi et al., 2009; Pietrangelo et al., 2009; Celletti et al., 2011, 2015, 2017a, 2017b;
140 Pazzaglia et al., 2016; Rabini et al., 2015; Attanasio et al., 2018), and in the presence of positive signs,
141 (spasticity, hypertonia, contractures, etc. (Camerota et al., 2011, 2016, 2017; Marconi et al., 2011;
142 Caliandro et al., 2012; Celletti et al., 2017b; Russo et al. 2019). In contrast, in such opposite
143 pathological conditions motor recovery could be commonly achieved by using deeply different and
144 highly specific physical exercises or pharmacological interventions.

145 This uncommon and, seemingly, paradoxical aspect is associated with other non-obvious findings,
146 highlighted in other studies, which show positive effects involving districts and functions outside of
147 the treated. RFV could, at least in part, attenuate a local functional deficit and this, in turn, could lead
148 to a development of new and more adequate compensatory strategies (Camerota et al., 2011, 2017;
149 Marconi et al., 2011; Pazzaglia et al., 2016). However, usually, compensatory strategies would develop
150 gradually, with a relatively long time, while improvement of muscular strength and/or power was
151 induced immediately (after 1 or 24 hours) in chronic patients (Brunetti et al., 2006; Filippi et al., 2009;
152 Celletti et al., 2012, 2017; Rabini et al., 2015). Body balance, mainly in closed eye conditions, (Brunetti
153 et al., 2006, 2015; Filippi et al., 2009; Rabini et al., 2015; Attanasio et al., 2018) largely improved.
154 Findings in chronic patients were often detected in the absence of any other physical therapy (Filippi
155 et al., 2009; Celletti et al., 2011, 2015; Brunetti et al., 2015; Rabini et al., 2015; Pazzaglia et al., 2016;
156 Attanasio et al., 2018; Russo et al., 2019). When RFV was integrated with a conventional rehabilitation
157 program, a powerful potentiating effect emerged compared with rehabilitation alone (Brunetti et al.,
158 2006; Marconi et al., 2011; Caliandro et al., 2012; Rabini et al., 2015). Improvements of the balance

159 in static (Brunetti et al., 2006, 2015; Filippi et al., 2009; Celletti et al., 2011, 2015; Attanasio et al.,
160 2015; Rabini et al., 2015; Pazzaglia et al. 2016) and dynamic conditions (Celletti et al., 2011, 2015;
161 Attanasio et al., 2015; Rabini et al., 2015; Pazzaglia et al., 2016) suggested the involvement of
162 untreated muscles and joints.

163 Unexpected effects have been observed even in the perception of position and movement, both for
164 the subjective straight ahead (Karnath, 1994; Kerkhoff, 2003) and for the velocity of body movement
165 (Pettorossi and Schieppati, 2014; Pettorossi et al., 2015), suggesting that intense proprioceptive
166 activation increases the perception of movement over time and changes the internal arrangement of the
167 spatial reference frame.

168

169 **Section 2: features of protocols for achieving the sensory-motor learning**

170 *2.1 Proprioceptive activation.*

171 The most common characteristics of the RFV used in the studies cited above includes oscillation
172 with vibratory frequency of 100 Hz and application time of at least 10 min. Direct evidence of the
173 effectiveness of these high frequency and duration was provided by different studies, also involving
174 the space perception after RFV (Pettorossi and Schieppati, 2014; Pettorossi et al. 2015). The magnitude
175 and persistence of the effect have been shown to be consistently observed using frequencies above 80
176 Hz and application time above more than eight minutes (Pettorossi et al., 2015).

177 Regarding the frequency 100 Hz, it is important to underline that this frequency is an appropriate
178 vibration frequency to stimulate the muscle spindles (Burke et al., 1976; Roll and Vedel 1982) and to
179 evoke the phenomenon of "spindle driving", i.e. Ia afferent discharge is driven at the same stimulation
180 frequency (Bianconi and Van Der Meulen, 1963). Thus, RFV at 100 Hz may drive the Ia afferent
181 discharge at the same frequency. Interestingly, such a frequency is often used to induce plastic
182 reorganization of central nerve networks, *in vitro* (Bliss and Lomo, 1973; Stanton and Sejnowski, 1989;
183 Bliss and Collingridge, 1993; Abraham and Williams, 2003) and *in vivo* (Iriki et al., 1989) by means
184 of an elevated glutamate synaptic release. This can lead to synaptic events such as LTP and result in
185 an immediate and sustained change in synaptic responsiveness, followed, later, by sustained
186 reorganization of the synaptic pathway.

187 Regarding the duration, it is well known that prolonged stimulation allows activation of
188 transcription and transduction of proteins that influence genomic expression at the nuclear level. The
189 activation of these mechanisms could explain the persistence of the effect over time (Lynch, 2004). *In*
190 *vitro* and *in vivo* studies show that stimulation (or training) must be repeated and organized in a spaced
191 training, i.e., over days, to allow optimal memory consolidation, which is superior to that achieved by

192 a massive training. Similarly, the consequence of intense sensory stimulation requires repetition over
193 consecutive days to ensure long persistence of the training-independent sensory learning (Smolen et
194 al., 2016).

195 In conclusion, the similarities between the characteristics of vibratory and *in vitro* stimulation
196 suggest that the effects of vibratory protocols may be fundamentally due to an LTP-like mechanism
197 that can develop plastic reorganization in the CNS.

198

199 2.2 Status of the vibrated muscle.

200 Another aspect to note concerns muscle status during vibration. In the reported studies showing
201 complex and sudden after-effects, the vibration was applied while the subject maintained the vibrated
202 muscle in a state of mild voluntary isometric contraction. In the absence of this condition, the results
203 were contradictory, showing either short (Fattorini et al., 2021) or no effects (Fattorini et al., 2006;
204 Brunetti et al., 2006, 2012, 2015; Marconi et al., 2008; Filippi et al., 2009, Pettorossi et al., 2015).

205 The apparently more effective results of RFV, applied on contracted muscle, seem to support the
206 mechanism of synaptic learning. Vibration coupled with voluntary activation of nerve circuits,
207 involved in the control of the treated muscle (expressed by muscle contraction), could be a typical
208 model of the Hebbian paradigm for inducing plastic changes in the central nervous system (Marconi et
209 al., 2008, 2011; Pettorossi et al., 2014, 2015). However, we cannot rule out that vibration effectiveness
210 is due to the stimulus power absorption by the biological system. Indeed, the stimulus transmission is
211 modulated by mechanical coupling and proprioceptive response. The former is related to the muscular
212 stiffness i.e. fibres recruitment and their length, promoting the transmission of vibrations by reducing
213 input damping and distortion. (Fattorini et al., 2016, 2017). The latter concerns the proprioceptive local
214 modulation managed by γ -drive able to regulate the spindle sensitivity (Burke et al, 1976).

215

216 **Section 3: Evidence of long-lasting excitability changes induced by RFV in the nervous circuits.**

217 Several studies have investigated the effects of muscle vibration on nerve circuits, exploring some
218 parameters of spinal and cortical excitability. Spinal excitability is affected by muscle vibration, as
219 shown by depression of the H-reflex after vibratory stimulation (Souron et al., 2017a; Rocchi et al.,
220 2018). These effects have been attributed to a decrease in motoneuron excitability by corticospinal
221 electrical stimulation studies (Souron et al., 2019). In addition, intense vibratory stimulation has been
222 found to induce both a decrease in spinal excitability and a cortical excitability modulation revealed
223 by comparing cortical *versus* thoracic or cervico-medullary evoked potentials (Kennouche, et al., 2022;
224 Pfenninger, et al., 2023). It should be noted that the duration of these spinal and cortical changes has

225 not been evaluated because the above studies were conducted under acute conditions. However, other
226 authors showed that H reflex and reciprocal spinal inhibition, after RFV, returned to baseline within
227 60 min (Rocchi et al., 2018).

228 As with spinal tests, several studies have reported changes in cortical excitability after muscle
229 vibration (Souron et al. 2017a). Acute effects, after a single session of FV, are equivocal regarding
230 cortical excitability, showing evidence of potentiation, decrease, or absence of effects in magnetic
231 evoked potentials (MEPs), short intracortical inhibition (SICI), intracortical facilitation (ICF)
232 (Rosenkranz and Rothwell, 2006; Souron, et al., 2017a; Kennouche, et al., 2022; Pfenninger, et al.,
233 2023). The reason for these discrepancies may be due to differences in the frequency, amplitude,
234 duration, and application modes of vibration (Rosenkranz and Rothwell, 2006). Conversely, studies on
235 chronic, long-lasting effects of RFV on the cortical excitability, are few (Marconi et al., 2008, 2011).
236 In these studies, on magnetic stimulation of primary motor cortex, before and after RFV, Marconi and
237 co-workers obtained long-lasting effects in both healthy (Marconi et al., 2008), and diseased subjects
238 (Marconi et al., 2011), showing a time course consistent with that described in section 1 (2-3 weeks,
239 the duration of follow-up). Furthermore, in the second work (Marconi et al. 2011) neurophysiological
240 tests were correlated with recovery of motor functions. Interestingly, these researchers applied RFV
241 protocol in tune with the parameters described in section 2 and used by the studies mentioned in section
242 1. Authors, in both the studies, evidenced a that short intracortical inhibition (SICI) changed
243 persistently increasing in the treated muscles, and decreasing in the untreated antagonist. Such a
244 rebalance, between agonist-antagonist muscles, suggests a specific and simultaneous up- and down-
245 regulation of intracortical GABAergic circuits (Marconi et al., 2008, 2011). In these experiments,
246 intracortical facilitation, motor threshold and H-reflex were tested. Intracortical facilitation did not
247 change, and the motor threshold decreased only in post-stroke patients (Marconi et al., 2011),
248 remaining unchanged in healthy subjects (Marconi et al., 2008). H-reflex, tested one hour after RFV
249 ending, was unchanged both in healthy and diseased individuals. This is not in contrast with Rocchi
250 and collaborators (2018), since they showed that the H-reflex returned to the baseline within 60 minutes
251 after RFV ending. Finally, in post-stroke patients, a significant and parallel correlation was shown
252 among SICI increase, threshold reduction and motor improvements. The authors suggested that cortical
253 changes could allow more efficient and selective muscle activation, associated with an improvement
254 in the role of the antagonist, which can reduce the mechanical impedance of the joint during the
255 movement (Marconi et al., 2008, 2011). A current view is that a SICI increase could lead to highly
256 coordinative abilities (Stinear et al, 2003; Dai et al., 2016; Mouthon and Taube, 2019), in healthy and
257 diseased individuals, to avoid the possible development of unwanted co-contractions and dyssynergia,

258 which could be an obstacle to movement (Liepert et al., 2000; Stinear et al., 2003; Marconi et al., 2011;
259 Dai et al., 2016; Mouthon and Taube, 2019).

260 A possible schematic sequence of these plastic changes, after RFV application, is shown in Figure
261 1. The cortex evidenced persistent rearrangements, that are temporally coherent with the behavioural
262 results reported in section 1, whereas the spinal excitability showed only transient change. Therefore,
263 the spinal cord excitability change does not seem relevant for long-term effects, even if it could initially
264 contribute to facilitate the induction of the persistent cortical plastic events.

265

266 **Discussion**

267 In this article, we argue that the motor improvements induced by RFV could find a possible
268 theoretical explanation in the ability of nonspecific sensory stimulation to induce long-term hetero-
269 and homo-synaptic effects in the CNS, such as LTP, and subsequent neural plastic rearrangements
270 (Beste and Dinse, 2013). This possibility was observed in the tactile, visual, and acoustic sensory
271 systems where were unspecific repetitive stimulation induced better discrimination of inputs (Pleger et
272 al., 2003; Frenkel et al., 2006; Clapp et al., 2012; Beste and Dinse, 2013). Beste and Dinse (2013)
273 referred to this mechanism as “learning without training”, to emphasize how the effects were not related
274 to the stimulus specificity. It is conceivable that similar learning can be observed in the proprioceptive
275 sensory system following RFV. This can be considered a form of proprioceptive training (Aman et al.,
276 2015) that can induce both a local increase of sensory discrimination and a central neural plasticity,
277 synergistically improving motor performance (flow chart of the effects is depicted in Figure 2). We
278 pointed out that RFV may generate synaptic potentiation in the proprioceptive circuits and can shift
279 the activity of neural circuits to a different level to enable the system to be more responsive and
280 adaptive. Evidence to support this adaptive mechanism of action is based on certain features of the
281 vibration stimulation protocol that are decisive in achieving functional benefits. The first piece of
282 evidence is the need to use high frequency vibratory stimulation. In fact, positive effects have been
283 observed only after the application of vibration frequencies above 80 Hz, up to 300 Hz, mostly 100 Hz
284 (Rosenkranz and Rothwell, 2004, 2012; Pietrangelo et al., 2009; Iodice et al., 2011; Pettorossi and
285 Schieppati, 2014; Pettorossi et al., 2015). Other authors reported that it is possible to induce positive
286 and persistent after-effects with prolonged and repeated stimulation and these are relevant parameters
287 for inducing plastic processes (Smolen et al., 2016). Furthermore, the effectiveness of RFV increases
288 when the subject pays attention to the area where the vibration is applied or it is associated with the
289 contraction of the activated muscle (Rosenkranz and Rothwell, 2012; Pettorossi et al., 2015). This

290 further supports the possible induction of heterosynaptic LTP, as occurs in Hebbian synaptic plastic
291 rearrangements (Hebb, 1949; Marconi et al., 2008, 2011).
292 Several studies have shown significant improvements in balance control, suggesting that RFV
293 increases proprioceptive circuit resolution. In fact, the improvement in balance control under closed-
294 eye conditions (Filippi et al., 2009; Celletti et al., 2011, 2015; Brunetti et al., 2012, 2015; Rubini et al.,
295 2015; Attanasio et al., 2018) and the changes in motion perception (Karnath, 1994, 2003; Pettorossi
296 and Schieppati 2014; Pettorossi et al., 2015) seem reasonably due to an enhanced ability of
297 proprioceptive signals to perceive position and motion. This could also be promoted by a refinement
298 of whole-body position and motion representation in space, in relation to spatial coordinates (Karnath,
299 1994, 2003; Pettorossi and Schieppati 2014; Pettorossi et al., 2015; Contemori et al., 2021). These
300 sensorial ameliorations might synergically act with central motor changes. On the other hand,
301 intracortical excitability shows the presence of different modulation of SICI relative to agonist and
302 antagonist muscles (Marconi et al., 2008, 2011). Consequently, joint stabilization can be more efficient,
303 by adapting the joint impedance to functional demands. In fact, appropriate modulation of joint
304 impedance can improve muscle strength, power, resistance to fatigue, as well as fluidity and precision
305 of movement. Fine-tuning of joint impedance is critical for the accuracy of motor execution and motor
306 learning. In addition, effective rebalancing of joint impedance, even if localized to a few joints, can be
307 instrumental in improving complex, multi-joint motor tasks, such as balance control and gait, and in
308 refining motor accuracy (Aprile et al., 2016; Contemori et al., 2021). Finally, the ability to optimize
309 functional joint stabilization and impedance is a key determinant of motor learning ability.

310 In conclusion, it seems evident that the shared features of stimulation protocols, proposed by
311 the studies cited above, could develop motor learning independent of training, which potentially opens
312 up new applicative possibilities. The present view suggests that appropriate proprioceptive stimulation
313 procedures may provide new perspectives, which can improve, and develop motor strategies even in
314 complex motor tasks, in which the proprioceptive modality is engaged.

315 It is to note that listed RFV studies involve mostly protocols adopting vibration frequency set
316 at 100 Hz. New researches are needed to verify the effective role of protocol characteristics in the
317 presence of different functional and pathological conditions and in combination with specific
318 rehabilitation training. These studies should consider the fact that vibratory stimulation should be
319 intense and reiterate and should exploit the combined activation of different signals to facilitate
320 synaptic potentiation through an hebbian mechanism. Furthermore, new experiments are needed to
321 directly confirm the neural changes elicited by high-frequency stimulation, possibly using strategies
322 able to interfere with the induction of short- and long-term synaptic changes.

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503

504 **Figure Legends:**

505 **Fig. 1.** Flow chart of RFV after-effects on nervous excitability. The suggested cascade of functional
506 implications is illustrated.

507 **Fig. 2.** The proposed RFV synaptic changes and the reported effects on the sensory system. The
508 possible increase of the motion perception and the improvement of the internal and external reference
509 system might favour motor planning and execution.

510

511 **Conflict of Interest**

512 The authors declare that the research was conducted in the absence of any commercial or financial
513 relationships that could be construed as a potential conflict of interest.

514 **Author Contributions**

515 GMF, AR, LF and VEP conceived the outline of the review. These authors contributed equally to this
516 work and share first authorship. MF and GR supervised project and provided suggestions to the
517 manuscript revisions. All authors have read and approved the final version of the manuscript and agree
518 with the order of the presentation of the authors.

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In review

Figure 1.JPEG

In review

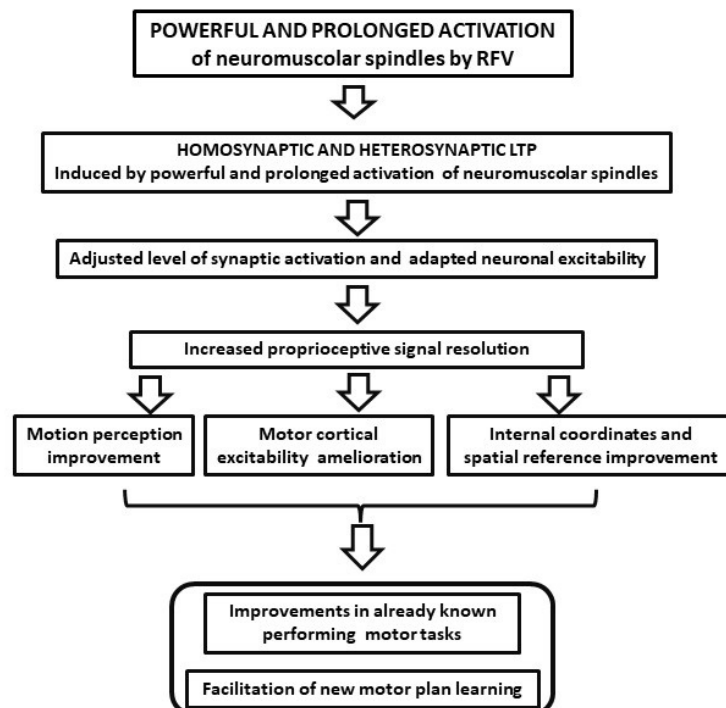


Figure 2.JPEG

In review

