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Editor's Comments: Freezing of gait (FOG) in Parkinson's disease (PD) patients is one of the least understood motor features of this condition but among the most disabling. Training patients to overcome FOG by using maneuvers to alter cognitive processing and sensory perception during ambulation is a common clinical approach to overcome this gait disturbance. Such techniques as stepping over a line on the floor or marching to a cadence result in moderate improvement at best. Here, Pereira, et al manipulate a single sensory modality, proprioception, through the application of vibration to muscle tendons in the lower extremities. In this experiment, they find that muscle vibration improves the severity and duration of FOG episodes, but only when applied to the least affected limb, suggesting that this technique may be less effective in more advanced basal ganglia disease. These results highlight the importance of sensory mechanisms in FOG and, importantly, stimulate thought on a new, potentially effective, therapeutic modality for this complication of PD.

Vincenzo Bonifati, Associate Editor, Erasmus MC, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands.

Freezing of gait in Parkinson's disease: Evidence of sensory rather than attentional mechanisms through muscle vibration

Marcelo P. Pereira [a, b, c], Lilian T.B. Gobbi [a], Quincy J. Almeida [c, *]

[a] Posture and Locomotion Studies Laboratory, UNESP – Univ Estadual Paulista, Physical Education Departament, Bioscience Institute, Rio Claro, SP, Brazil
[b] Research Group for Neuromotor Rehabilitation, Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium
[c] Sun Life Financial Movement Disorders Research and Rehabilitation Centre, Wilfrid Laurier University, Waterloo, ON, Canada

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ABSTRACT

Introduction: The role of proprioceptive integration impairments as the potential mechanism underlying Freezing of gait (FOG) in Parkinson's disease (PD) is still an open debate. The effects of muscle vibration (a well-known manipulation of proprioception) could provide the answer to the debate. The aim of this study was to determine whether proprioceptive manipulation, through muscle vibration, could reduce FOG severity.
Methods: Sixteen PD patients who experience FOG were required to walk with small step lengths (15 cm). Cylindrical vibration devices were positioned on triceps surae tendon. Three vibration conditions were tested: No vibration (OFF), vibration on the less affected limb (LA), or on the more affected limb (MA). Additionally, we assessed the effects of applying vibration before and after FOG onset. The FOG duration and the foot used to take the next step were assessed.
Results: FOG significantly decreased only with vibration of LA in comparison to OFF, and when vibration was applied after FOG onset.
Conclusion: Our results show that muscle vibration is a promising technique to alleviate the severity of FOG. Improvements to FOG behavior were restricted to the less affected limb, suggesting that only the less damaged side of the basal ganglia may have preserved capacity to process sensory feedback. These results also suggest the likelihood of sensory deficits in FOG that cannot be explained by cognitive mechanisms, since vibration effects were only observed unilaterally.
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1. Introduction

Freezing of gait (FOG) is one of the most debilitating symptoms in Parkinson's disease (PD) [1] and it is defined as *'brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk'* [2]. The mechanisms underlying FOG are not fully understood [3], however, sensory-perceptual (and specifically proprioceptive processing) deficits seem to play an important role in this phenomenons occurrence [4–7]. Ehgoetz Martens et al. (2013) found a higher number of FOG episodes when PD patients relied primarily on proprioception to walk through a doorway [5]. However, when extra visual feedback was given, the number of FOG episodes profoundly decreased [5]. This supports the notion that sensory-deficits profoundly influence FOG episodes [4,6,8]. In

* Corresponding author. Wilfrid Laurier University, Northdale Campus, 66 Hickory Street, Waterloo, ON, N2L 3J5, Canada.
E-mail address: qalmeida@wlu.ca (Q.J. Almeida).

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agreement, Tan et al. showed that patients who experience FOG (PD-FOG) have poorer performance when force-matching, especially when proprioceptive feedback was artificially disturbed by vibration. An internally generated cueing deficit was suggested to be responsible to higher force-match errors in PD-FOG [6]. Therefore, since locomotion also relies on internally generated cueing information, the authors suggested that FOG episodes could be the result of impaired sensory processing primarily arising from the proprioceptive system [6].

In order to investigate the role of proprioception on the FOG occurrence/severity a study-design that could manipulate the proprioceptive system during FOG episodes were developed. To manipulate proprioceptive feedback, previous studies have used muscle vibration on lower limbs and/or torso muscles [9–11]. The physiological effects of muscle vibration has been already extensively described, but briefly, vibration elicits stimulation of muscle spindle 1a sensory fibers [12,13], leading to an illusory stretching sensation [14] and to a contraction of antagonistic muscles [12,14]. Muscle vibration can be used to disturb or to facilitate movement. For example, in the study of Tan et al. (2011), during an isometric knee extension task, vibration was applied on the patellar tendon, leading to an illusory knee flexion sensation [6]. In other words, vibration created an illusory sensation in the opposite direction (knee flexion) to the target task (knee extension). As a final result, vibration lead to an undershoot force-matching performance with the use of vibration [6]. In the same way, during gait, vibration of the tibialis anterior (that elicits a backward body displacement sensation [9] – opposite to ongoing movement direction) lead to decreased step length in PD [15]. In contrast, the vibratory stimulation of posterior lower limb or back muscles (that creates an illusory forward body displacement sensation [9] – in the same direction of ongoing movement) has been shown to improve gait performance in PD patients [15–17]. Hence, vibration can be applied to facilitate (when elicits illusory sensation in the same direction of ongoing movement) or to disturb the proprioceptive system. Finally, previous research have uncovered the positive effects of other forms of sensory stimulation in alleviating and preventing FOG, such as visual and auditory cueing [18–20]. All these findings, taken together, suggest that sensory stimulation, specifically in the proprioceptive domain may be an interesting tool to alleviate/prevent FOG. Yet to our knowledge, the direct effects of proprioceptive stimulation on the severity of FOG episodes, has never been tested.

Additionally, considering the asymmetrical basal ganglia degeneration observed in PD [21], manipulating the limb stimulated by vibration could raise greater insight into the role of sensory-processing deficits in individuals who experience FOG. Maschke et al. (2003) demonstrated that the more affected limb also displayed worse kinesthesic ability compared to the less affected limb during a passive joint movement detection test [22]. Since correlation analyses revealed a close relationship between the motor subsection of the Unified Parkinson's Disease Rating Score (UPDRS III) and the movement detection deficit, the authors argued that the more degenerated the basal ganglia the worse the proprioceptive processing capacity [22]. Hence, we hypothesized that isolated stimulation of the less (compared to more) effected lower limb would provide greater insight into the role of proprioceptive processing capacity during the occurrence of FOG. We hypothesized that proprioceptive-stimulation of the less affected lower limb would result in shorter periods of motor blocks compared to stimulation of the more affected limb, since according to Maschke's et al. (2003) results, the less affected basal ganglia has a more preserved capacity to process proprioceptive information. In line with this perspective, if sensory processing deficits underlie FOG, we would expect an absence of response to vibration or a more discrete reduction of motor blocks duration with the proprioceptive stimulation of the more affected limb. Considering all points discussed here, the main aim of this study was to investigate the effects of muscle vibration applied on the posterior lower limbs muscles on FOG episodes severity (e.g.: duration of episodes) when it was applied in both preventive and alleviative fashion. As hypothesis, we believe that improving proprioceptive feedback inflow to the central nervous system could improve sensory processing deficits, thereby reducing the severity of FOG episodes. Additionally, we aimed to investigate the effects of stimulating the less and more affected lower limb on FOG severity. As stated previously, we believe in more concrete results only when the less affected limb is proprioceptive-stimulated.

2. Methods

2.1. Participants

Eighteen PD patients that experience FOG were recruited to participate in the study. To be included, patients had a previous clinical diagnosis of idiopathic PD. The potential presence of FOG was identified using UPDRS-II (activities of daily life: self-reported) [5], and then confirmed by a clinical walk assessment procedure involving turns, and walking through doorways as previously described by Almeida et al. [4–8]. In addition, as exclusion criteria, patients did not have important co-morbid conditions that could influence the study (e.g.: history of stroke, visual impairments, hearing loss, peripheral neuropathies, diabetes and dementia). UPDRS III (motor evaluation) was used to assess the participants' motor disabilities. The Montreal Cognitive Assessment (MoCA) scale screened the participants' cognition level and a score <26 was considered as a cut-off point [23]. From the eighteen patients invited to participate, two were excluded due to dementia and/or high severity of motor symptoms (inability to perform the task without external assistance). Therefore, a total of 16 PD-FOG were assessed (fourteen males; UPDRS-III: 25.73 ± 3.10 points, age: 70.71 ± 7.77 years; MoCA: 25.73 ± 3.10 points). All participants gave written consent prior the participation in the study and all procedures were approved by the Local Ethical Committee.

2.2. Experimental setup

All assessments were done during an optimal "on-phase" of the medication (~1.5 h after the medication intake). In order to optimize the number of participants that would agree to participate and complete the study, the choice to assess the participants in the ON medication phase was based on the results of pilot studies: where in some cases, participants were not able to complete the task in the OFF phase of medication. In order to investigate the effects of local vibration in FOG severity, it was necessary to elicit FOG episodes. To that end, we used an adaptation of the sequence effect paradigm described by Chee et al. (2009): all participants were asked to walk 5 m on an electronic walkway (Zeno Walkway – ProtoKinetics®) at their self-selected pace using a 15 cm step

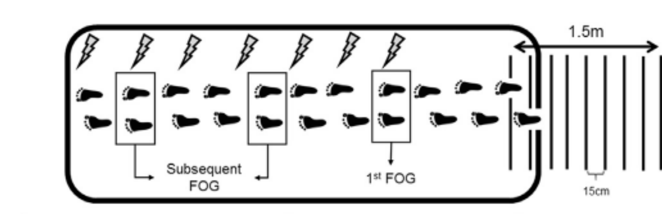

Fig. 1. Experimental set-up. Note that vibration was not switched on before the first FOG onset. Vibration was kept on until the end of the trial.

length. A total of ten stripes were positioned on the floor, perpendicularly to the walkway, to be used as visual cues of the required step length (Fig. 1). In order to avoid any possible effect, eight stripes were positioned prior to the data collection area. Therefore, participants were asked to step on each stripe consecutively, and to keep the same step length until the end of the pressure-sensitive mat – Fig. 1. Participants were also instructed to walk 2.5 m beyond the end of the mat, to avoid slowing down.

Vibration was applied on the triceps surae tendon by custom-made vibratory devices (constructed using steel DC micro motors bearing eccentric masses; devices measures: 4.5 cm × 2 cm × 2 cm, 27–3 g) fixed by elastic bands. An electronic board (which was worn as a belt and controlled via Wi-Fi) was used to control the vibratory devices. This system allowed the participants to walk freely during the experiment. The same optimal vibration parameters usually used in the literature for healthy and PD patients [15,16,24] were chosen: 100 Hz and 1.2 mm of amplitude. These parameters are often used regardless the muscle being stimulated.

2.3. Procedures and data analysis

Three conditions (randomly distributed in blocks) were compared to evaluate the effectiveness of vibration to reduce FOG severity (duration of FOG episode): (i) without vibration (OFF), (ii) vibration on the less affected limb (LA) and (iii) vibration on the more affected limb (MA). The definition of the less and more affected limb was based on the clinical assessment and asymmetry identified during the Unified Parkinson's Disease Rating Scale subsection III (UPRDS-III). During LA and MA, vibration was switched on manually by the experimenter on the first detectable FOG episode onset and kept on until the end of the trial. Therefore, it was possible to assess two different vibration effects on FOG severity: (i) an "alleviative" vibration effect: during the occurrence of the first FOG episode, where the vibration was switched on after the FOG onset; (ii) a "preventive" vibration effect: wherein the vibration was already switched on before the FOG onset (Fig. 1). Each participant performed four trials of each condition, independently of number of trials that FOG episodes were observed. Therefore, each participant performed twelve trials.

FOG episodes were defined as episodes lasting longer than 1 s wherein the participants were unable to continue the ongoing walking [4]. Since the experimental set-up demanded an online decision of when a FOG episode occurred, off-line confirmation of the occurrence of FOG was necessary. To that end, the projection of center-of-mass velocity (assessed by the PKMAS software – ProtoKinetics®) was evaluated. Only those episodes wherein the center-of-mass projection velocity reached zero (meaning a complete arrest in gait behavior) were considered for further analysis. FOG episodes shorter than 1 s were not included in the final analysis. These procedures ensured that pure shuffling (i.e. gait with continuous but constant small amplitude steps) were not considered. After applying these procedures, a total of eight false FOG episodes were excluded from further analysis. The FOG severity (FOG duration) was assessed as the time between the initial foot contact before and after the FOG occurrence. Additionally, we assessed the time between FOG episodes for all conditions – this allowed us to check the effects of vibration on preventing the manifestation of new FOG episodes. In the LA and MA conditions, the limb used to take the next step after the FOG breakdown was also assessed.

Considering the difficulty to elicit FOG episodes in a research environment, the number of trials with FOG episodes across participants was not the same. Therefore, we averaged the duration of FOG episodes across conditions and across participants. To assess the acute and preventive effect of vibration on the severity of FOG episodes, two separate repeated measure ANOVAs were conducted, considering each condition as a fixed factor. In the first analysis, we considered only the first FOG episodes duration. In the second analysis, all the subsequent FOG episodes (excluding the first one) were considered. In this last case, for OFF we also excluded the first FOG episode duration. Whenever necessary, a Tukey post-hoc test was used to assess further differences between conditions. For those ANOVAs that reached statistical significance we assessed the effect size of paired comparisons using the Cohen's d for within-subjects design [25]. According to Cohen (1988), the effect size can be considered as low ($d = 0.2$), medium ($d = 0.50$), large ($d = 0.80$) or very large ($d = 1.30$). Also, in order to investigate the effect of the limb stimulated by vibration in the foot used to take the following step we used a Chi-square test.

3. Results

A total of 102 FOG episodes were observed: 29 as the first FOG episode and 73 as subsequent episodes.

A main effect of condition was observed for the first FOG episode duration Fig. 2 ($F_{(2,5)} = 4.36$, $p = 0.04$, $\eta_p^2 = 0.466$), whereas the post-hoc test showed that only in LA the acute effect of vibration reduced the severity of FOG episodes (LA *vs* OFF: $p = 0.038$; $r = 0.24$; $d = 1.66$). Similarly, results revealed that MA was not different from both OFF ($p = 0.174$; $r = -0.33$; $d = 0.62$) and LA ($p = 0.623$; $r = -0.22$; $d = 0.59$). This means a very large effect size for the LA *vs* OFF comparison and a medium effect size among other comparisons [26].

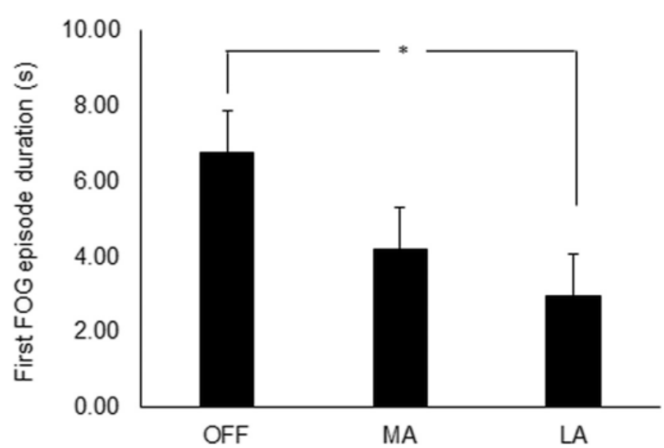

Fig. 2. Mean duration (and standard error) of the first FOG episode during the three assessed conditions: OFF: no vibration; MA: vibration on the more affected limb; LA: on the less affected limb. *$p < 0.05$.

For the subsequent FOG episode durations (Fig. 3), the repeated-measure ANOVA found only a marginal effect ($F_{(2,5)} = 3.71$, $p = 0.062$, $\eta_p^2 = 0.426$). However, since a moderate-to-high effect size was observed, a Tukey post-hoc test was completed. A marginal effect, showing that vibration failed to prevent FOG was found, since the FOG duration while walking with vibration was close to being longer in MA than in OFF ($p = 0.071$) and was not different in LA in comparison to OFF ($p = 0.930$). There was no difference between MA and LA ($p = 0.127$). Vibration also was unable to reduce the time spent between FOG episodes (OFF: 3.67 ± 1.12s; MA: 3.20 ± 0.2.41s; LA: 2.39 ± 1.52s; $F_{(2,5)} = 1.28$, $p = 0.31$, $\eta_p^2 = 0.203$), highlighting then non-effective impact of vibration as a preventive tool.

From the 102 FOG episodes, 55 were observed in LA and MA conditions. From the 55 episodes, 54.55% were observed in LA and

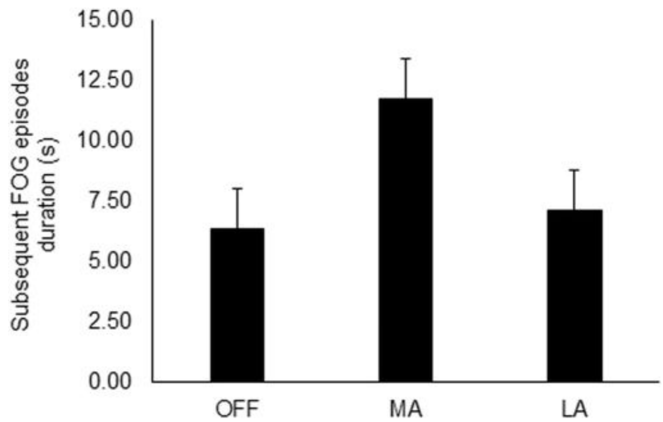

Fig. 3. Mean duration (and standard error) of the subsequent FOG episodes during the three assessed conditions: OFF: no vibration; MA: vibration on the more affected limb; LA: on the less affected limb.

45.45% in MA. Also from the total of 55 episodes, in 38.18% participants used the same limb that were being stimulated to take the next step and in 61.82% of the trials, they used the contralateral limb to take the next step ($X^2 = 4.026$; $p = 0.044$). This result shows that vibration influenced the limb used to reinitiate gait.

4. Discussion

The main aim of this study was to investigate the effects of an artificial stimulation of the proprioceptive system, through tendon vibration, on the severity of FOG episodes in PD patients. No positive effects of local muscle vibration were identified when vibration was applied before the FOG onset, showing that these sorts of devices may not be useful as a preventive strategy. In fact, our results suggest a FOG severity detriment when vibration was applied before its occurrence. However, our results clearly show that FOG is alleviated by vibration if it is applied after FOG onset and in the less affected lower limb. Our results also highlight the importance of recognizing sensory mechanisms that may underlie FOG in PD, even though this was not our main objective.

Previous studies have suggested that local vibration applied on both torso or lower limbs improves gait in PD patients [15,17,27]. In this way, we hypothesized that patients that experience FOG could also be benefited by local vibration. However, our intention was not only to investigate if vibration could improve PD-FOG gait, but rather, our main aim was to investigate if local vibration could alleviate FOG episodes. Confirming the initial hypothesis, our results clearly show that vibration applied after the FOG episodes onset alleviates its severity. A few mechanisms may be pointed as responsible for the positive influence of vibration: (i) a cue-related effect, (ii) issues related to cognitive/attentional resources and (iii) an enhanced proprioceptive processing.

The positive effects of visual and auditory cueing on FOG has been already demonstrated by others [18,19]. Previous studies suggested that cues may help patients in maintaining the gait automaticity [3,19] and therefore, avoiding the accumulation of motor deficits responsible for FOG episodes [28]. In this way, it might be argued that participants could have used vibration as an external cue: i.e. auditory or step-synchronizing cue. However, if vibration served as an external cue we would had observed fewer episodes of FOG after the vibration onset, since it would diminish the sequential detriment of walking rhythm responsible to elicit FOG [28]. However, a high number of FOG episodes (n = 42) was observed when vibration was already on: 41.17% of the total and 76.36% of FOG episodes wherein vibration was used. In agreement, if vibration was used as an auditory or step-synchronizing cue, subjects would also be positively affected by the stimulation of the more affected lower limb, but this also was not the case in the current study.

Alternatively, an argument could be made that cognitive/attentional mechanisms might explain the positive effects of vibration. Previous research has shown that FOG episodes could be the consequence of reduced central processing resources to deal with conflicting information [3]. According to this theory, vibration could have shifted patients' attention to the lower limb when they were stimulated by vibration and helped them to focus on what do next: to take the next step. However, if this was the main mechanism underlying our results, we would expect a positive effect also when the more affected lower limb was stimulated. Since peripheral somatosensory processing is not impaired in PD patients [29], we suggest that proprioceptive perception would also trigger attentional processing when the more affected limb was stimulated. Finally, if attentional mechanism could explain our results, we would have expected that the majority of the first step after FOG would be taken by the stimulated lower limb. However, in 61.82% of the trials when vibration as used, the next step was taken with the contralateral lower limb.

Therefore, the current results most strongly support enhanced proprioceptive information processing as the mechanism underlying our results. According to Tan et al. (2011), PD-FOG have a deficit in internal cueing [6], reducing the internal rhythm generation [30]. In agreement with this statements, Ehgoetz Martens et al. (2013), found a higher number of FOG episodes when patients relied only on proprioception [5]. Finally, also agreeing with this theory, Tan et al. (2011) found a worsening in a force-match task performance in PD-FOG when proprioception was disturbed [6]. Therefore, since local vibration is known as an artificial way to stimulate the proprioceptive system, it is believed that this stimulation played a major role in reducing the FOG severity episodes, when it was applied after the FOG onset.

Recently, a brain imaging study showed that during upper limb motor blocks, PD patients that experience FOG present a higher motor cortex activation in comparison to non-FOG patients [31]. This last study also suggested that this increased cortical activation level during the motor block was the consequence of a late response to restore movement [31]. Rosnkranz et al. (2003) showed that local vibration induces a selective and focused motorcortical activation of the vibrated area [32]. Therefore, we suggest that vibration, when switched on after the FOG onset, worked as a flashlight pointing to specific brain regions that needed to be recruited and activated, ameliorating the motor breakdown. Separately, the study of Vercruysse et al. (2014) also showed a reduced activation level in dorsolateral prefrontal cortex, dorsal premotor cortex and in motor cortex before the motor block onset [31]. It was suggested that this reduced activation level before the motor block was a hyperinhibitory response from the subcortical structures seeking for inhibition of nonselective action programs [31]. This theory may explain why vibration did not have positive effects when applied before FOG onset. Since local vibration leads to a higher activation level in the motor cortex [32], when it is applied before FOG onset, it may have increased the number of nonselective action programs, requiring an even higher inhibitory subcortical level. As consequence, PD-FOG may have experienced an even later activation of the motor cortex, thereby worsening subsequent FOG episodes severity. These theories remain speculative and of course should be further investigated in the future.

However the positive effect of vibration only on the less affect lower limb supports the cortical involvement in the mechanisms underlying our results. Since PD is an asymmetrical disease [21], it is suggested that the most impaired basal ganglia was not able to properly process the proprioceptive stimulation driven by vibration. In contrary, when the less affected limb was stimulated, a more preserved basal ganglia was able to process properly the enhanced information, thereby reducing FOG episodes severity.

Taken together, our results highlight the involvement of an impaired sensory processing deficit in FOG episodes occurrence. However, the main aim of this study was to investigate whether local muscle vibration could be used as an alternative rehabilitation tool to alleviate FOG severity. Our results clearly show that vibration applied after the FOG onset can reduce its duration. Some study limitations are obvious, as the low number of patients that presented FOG episodes ($n = 6$). However, we found moderate-to-high vibration effect size ($\eta_2^2 = 0.466$) showing that type II error is not responsible for our results. In addition, the examiner manual vibration triggering method could have influenced the time patients remained frozen, biasing the results. However, since FOG duration was higher in OFF, an automatic vibration triggering method would have reduced even more the FOG duration. Finally, we were unable to assess the participants in the OFF-medication state, since they were unable to perform the task in this condition. However, there is evidence supporting that proprioceptive abnormalities in PD are not overcome by dopamine replacement [22,33,34]. Hence, we do not believe that a different result would be found if the participants had been assessed in the OFF state; however this is speculative and should be tested in future studies.

5. Conclusion

In conclusion, vibration applied on the gastrocnemius tendon of the less affected lower limb after the FOG episodes onset, reduces its severity. When it is applied before the FOG occurrence, vibration does not have positive effects. Enhanced proprioceptive feedback is an important therapy that requires further investigation in FOG patients, and the results of the current study highlight the involvement of sensory deficits in the mechanisms underlying FOG.

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