Balancing between the two: are freezing of gait and postural instability in Parkinson's disease connected?

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ABSTRACT

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Postural instability and freezing of gait (FoG) are key features of Parkinson's disease (PD) closely related to falls. Growing evidence suggests that co-existing postural deficits could influence the occurrence and severity of FoG. To date, the exact nature of this interrelationship remains largely unknown. We analyzed the complex interaction between postural instability and gait disturbance by comparing the findings available in the posturographic literature between patients with and without FoG. Results showed that FoG and postural instability are intertwined, can influence each other behaviorally and may coincide neurologically. The most common FoG-related postural deficits included weight-shifting impairments, and inadequate scaling and timing of postural responses most apparent at forthcoming postural changes under time constraints. Most likely, a negative cycle of combined and more severe postural deficits in people with FoG will enhance postural stability breakdown. As such, the wide brain network deficiencies involved in FoG may also concurrently influence postural stability. Future work needs to examine whether training interventions targeting both symptoms will have extra clinical benefits on fall frequency.

KEYWORDS

Parkinson's disease, Freezing of Gait, postural control, posturography

1. INTRODUCTION

Balance impairment and an increased fall risk are among the most debilitating symptoms in patients with Parkinson's disease (PD). Previous work reported prevalence rates of 35% up to even 90% of yearly falls in patients with PD (Allen et al., 2013). Eighteen to 65% of these fallers become recurrent fallers when the disease progresses (Allen et al., 2013), although falls may taper off again in the final disease stages when patients become progressively immobilized (Pickering et al., 2007). Both disease severity itself (inability to walk), handicaps from physical injuries and fear of falling contribute to this immobility (Bloem et al., 2006), thus inducing a vicious circle. As such, investigating the causal factors of falls as well as potential methods for fall prevention is of great importance. Falls in PD mostly occur during turning (24%), bending forward (16%) and standing up (15%) (Bloem et al., 2001), and usually happen unrelated to dominant environmental hazards, but rather to self-induced movements of the center of mass (CoM). Previous studies already identified several predictors of falls in PD. Unstable posture and sudden loss of postural reflexes were found to be one of the main associated factors in 55% of falls (Factor et al., 2011; Michalowska et al., 2005). Freezing of gait (FoG) together with postural instability explained approximately 80% of falling (Michalowska et al., 2005).

FoG is defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (Nutt et al., 2011). FoG is present in about 27% of PD patients in the very early disease stages and its occurrence increases to up to 86% in the advanced stages (Giladi et al., 2009; Tan et al., 2011a). It is triggered by specific situations like gait initiation, turning, narrow passages, obstacle crossing or approaching a destination (Nutt et al., 2011; Schaafsma et al., 2003). Differently put, FoG occurs during voluntary displacement of the CoM or when a flexible change between postural sets is required. Freezing episodes are often described as 'the feeling that the feet are being glued to the floor' while the trunk continues to move forward (Mahabier et al., 2010), illustrating that the CoM is sometimes misaligned with the rest of the body, or vice versa, that movement cycles cannot keep up with the CoM. Understanding the exact interaction between FoG and postural control will inform the development of specialized training interventions to ameliorate the specific postural control deficits

related to FoG, potentially impacting on falls (Mak et al., 2017). Therefore, this narrative review aims to unravel this interaction based on the currently available posturographic literature in PD.

1.1. Framework of postural control in PD

Postural control is a very complex system consisting of many different subcomponents (Horak, 2006): biomechanical constraints including limits of stability and strength, movement strategies used to return body to equilibrium, sensory strategies to integrate or reweight the information of the visual, vestibular and somatosensory systems, cognitive processing, balance control during gait and dynamic movements. Disorders in any of these subcomponents may be the cause of balance problems and falls in PD. Schoneburg and colleagues introduced a framework describing different aspects of postural control specifically in PD (Schoneburg et al., 2013). First, we will discuss these aspects of postural control and their possible relationship with or relevance for FoG. Afterwards we will compare the performance of freezers and non-freezers on each component of this framework in detail in section 3.

1.1.1. Quiet stance

In order to maintain a stable posture, the body relies on information coming from visual, vestibular and proprioceptive input. The contribution of each input system varies and depends on age, the presence of pathology and the postural challenge, also called ‘sensory reweighting’ (Horak, 2006; Peterka, 2002). Basal ganglia dysfunction has been hypothesized to play a role in the abnormal integration of sensory information, likely contributing to various postural abnormalities, impaired sensory orientation and altered sensory reweighting observed in PD (Conte et al., 2013; Horak et al., 1996; Jacobs et al., 2005; Konczak et al., 2009; Schoneburg et al., 2013). Interestingly, sensory-motor integration difficulties were found particularly in patients with FoG in a variety of motor tasks suggesting an interaction of FoG and quiet stance instability related with altered sensory reweighting (Almeida and Lebold, 2010; Ehgoetz Martens et al., 2014; Ehgoetz Martens et al., 2013; Huh et al., 2016; Nantel et al., 2012; Pereira et al., 2016; Tan et al., 2011b). For quiet stance, the below review focusses on aspects of sensory reweighting and limits of stability separately.

1.1.2. Reactive postural control

Postural reactions to perturbations are considered automatic responses, as the activation onset of muscle contractions is shorter than voluntary reaction times (Rinalduzzi et al., 2015). In response to perturbations, postural abnormalities have been identified in PD including inflexible, ineffective and delayed balance correcting responses (Bloem et al., 1996; Carpenter et al., 2004; Dietz et al., 1988; Dimitrova et al., 2004; Horak et al., 2005; Horak et al., 1996; Horak et al., 1992; King and Horak, 2008; King et al., 2010). Freezers seem to have even greater impairments in movement automaticity than non-freezers (Nutt et al., 2011; Vandenbossche et al., 2012), suggesting that FoG may also be related with impaired reactive postural control.

1.1.3. Anticipatory postural adjustments

Anticipatory postural adjustments (APAs) are necessary adjustments prior to movement to maintain stability by compensating for anticipated destabilization associated with moving a limb. For gait, APAs in center of pressure (CoP) data have been defined as shifts of the CoP posteriorly and laterally prior to gait initiation so that the swing leg is loaded first and then freed for stepping forward. Jacobs et al. (2009) were the first reporting that freezers showed multiple and inappropriate APAs preceding reactive stepping, which were also accompanied by trembling of the knees, similar to the oscillatory behavior during a FoG episode (Jacobs et al., 2009b). This led to the influential hypothesis that freezing might reflect impaired coupling between an APA and the stepping command (Jacobs et al., 2009b; Nutt et al., 2011). What is still unclear is whether postural instability during an APA, the delayed stepping generation alone or the two mechanisms together, determine this coupling problem.

1.1.4. Dynamic postural control

The transfer of body weight between legs (weight shifting) also forms the basis for locomotion. The ability to control balance during continuously changing conditions is called dynamic postural control. Walking has been studied extensively in the context of FoG and has shown abnormalities outside the realm of the episodes itself (Nonnekes et al., 2014b; Plotnik et al., 2012; Williams et al., 2013). Alternated loading and unloading of the legs is also required during movements such as stepping in place and turning. The latter requires additional adaptation to asymmetrical circumstances and body

rotation (Plotnik et al., 2008). During turning, worse bilateral coordination has been reported in freezers compared to non-freezers (Peterson et al., 2012) and freezing episodes have been triggered most consistently during rapid 360-degree narrow turns (Schaafsma et al., 2003; Snijders et al., 2012), suggesting that FoG is related with the dynamic postural control aspect of weight shifting.

1.2. Models of the relationship between postural instability and FoG

A recent meta-analysis showed that postural performance as detected by clinical balance scales was significantly and consistently worse in freezers compared to non-freezers (Bekkers et al., 2017). However, whether this overlap was incidental and merely related to disease progression could not be established. Although postural instability and FoG frequently (but not necessarily) co-occur, it is still unclear whether both symptoms have shared pathological mechanisms (Bloem et al., 2004). **Figure 1** illustrates three possible models to explain this co-occurrence.

Model I, the independent model, displays FoG and postural instability as two independent phenomena whereby patients present with one or the other symptom, irrespective of the other (Nonnekes et al., 2015).

Model II, the consequence model, describes postural instability and FoG as neurologically two independent phenomena, but considers the possibility that FoG is behavioral interference. For example, increased postural instability may be a consequence of FoG, as was described above when stepping of the feet is not followed by the CoM forward progression. The opposite is also possible, namely that inflexible postural behavior underpins FoG. For instance, en-bloc turning may exacerbate inefficient unloading of the swing limb, triggering an episode. In clinical practice, ambiguous cases may also arise. A patient may show an aberrant pull test due to ‘freezing’ of a protective stepping response, whereas postural stability is otherwise normal. Hence, the presence of freezing may sometimes mask normal postural reactions and lead to occasional misinterpretation.

Model III, the overlap model, offers an alternative prospect, namely that postural instability and FoG are truly overlapping phenomena which impact upon each other to a lesser or greater degree due to common underlying pathophysiology. Arguments supporting such a close relationship are the fact that

both are seen more often in the later disease stages, respond poorly or paradoxically to dopaminergic medication and have an episodic and unpredictable nature (Bloem et al., 2004; Factor et al., 2011).

[Insert Figure 1]

The current review will first discuss the behavioral findings of postural instability and their interaction with FoG, aiming to synthesize these two areas of study into a conceptual model illustrating this complex relationship.

2. METHODS

For the purpose of this review, we only included studies comparing postural control between PD patients with and without FoG. We used MEDLINE to search for references up to December 2017, based on the following search terms in the title and/or abstract: ‘freezing of gait’ or ‘freezer*’ in combination with ‘posture’, ‘postural’, ‘balance’, ‘stability’ or ‘turning’. Relevant articles were identified based on screening of titles, abstracts and full-texts. Also, relevant papers cited by these articles were explored. Two explicit inclusion criteria for selection were adopted: (i) studies comparing between PD patients with and without FoG and (ii) studies assessing performance-based balance outcomes using posturographic techniques. Posturography is defined as encompassing all techniques used to quantify postural control during upright stance, in both static and dynamic conditions (Furman JM, 1993; Visser et al., 2008). Posturographic tools mainly capture measures of postural sway, which are the continuous small corrective movements that are made by the upright body to maintain equilibrium. These are often quantified by motion properties of the CoP or the CoM obtained from force-plates, inertial sensors or 3D motion analysis.

We summarized studies in four sections. First, we looked at quiet stance, in which we included aspects of sensory orientation and limits of stability separately. Next, we examined 2) reactive postural control, 3) anticipatory postural control and 4) dynamic postural control. As for the latter, we only included posturographic data captured during turning, self-initiated stepping and voluntary alternating weight-

shifting during stepping in place. In these tasks, we assessed CoM and trunk movements and step width, reflecting typical postural control rather than gait parameters (Lord et al., 2013).

Additional exclusion criteria were studies which only analyzed freezers or solely compared freezers with healthy controls. We also disregarded studies published in abstract form. Hence, data were extracted based on full-text articles. Postural outcomes which differed significantly between freezers and non-freezers are presented in Tables 2-5. The most important non-significant postural parameters are listed in a separate column. A methodological analysis of the included studies was conducted to determine whether the differences between freezers and non-freezers were freezing-specific or were influenced by disease confounds (**Table 1**).

3. RESULTS

The review revealed 27 studies including in total 460 freezers and 485 non-freezers. Reported mean ages ranged between 58 and 75.3 years old in the freezers and between 60 and 74.7 in the non-freezers (**Table 1**). All studies adopted different criteria for defining a freezer. Patients across different disease stages were included, ranging between Hoehn & Yahr (H&Y) stage I-IV. Table 1 shows that the disease characteristics differed significantly between FoG subgroups in 13 out of 27 studies, and were reported incompletely in 18 of the 27 studies. Only 2 studies accounted statistically for these group differences. Cognitive profiles were reported in 17 studies, two of which reported cognitive scores to be significantly lower in the freezer group. The levodopa equivalent dosage (LED) was significantly higher in freezers in 3 out of 10 studies. Seventeen studies did not provide details on medication intake and 16/27 studies were performed OFF medication. All studies provided details about age, which was well-matched between groups. In the next sections, the most important results will be summarized per component of postural control of the Schoneburg framework, although sometimes an overlap between the different domains is apparent.

3.1. FoG and quiet stance

3.1.2. Upright posture

Table 2 shows that 5 out of 8 studies, investigating quiet standing with eyes open did not find differences between freezers and non-freezers (Ehgoetz Martens et al., 2016; Huh et al., 2016; Nantel and Bronte-Stewart, 2014; Pelykh et al., 2015; Vervoort et al., 2013). The two studies with the largest population reported abnormalities in the anterior-posterior (AP) direction both in the ON as in OFF phase. Freezers shifted their CoP position more backward than both non-freezers and controls (Schlenstedt et al., 2016) and showed increased AP sway dispersion (as expressed by the Root Mean Square of postural sway) compared to non-freezers (de Souza Fortaleza et al., 2017). These findings coincided with the result that also AP CoP range was found to be increased in freezers (Kim et al., 2016). We conclude that quiet standing is largely similar between PD subgroups, but the susceptibility for backward postural instability in people with FoG is increased.

3.1.2 Limits of stability

Table 2 also demonstrates that patients with FoG showed a reduced ability in voluntary leaning in forward and backward directions expressed as limits of stability (LoS) outcomes. Reduced LoS peak distances and reduced anterior CoP displacement, also proved correlated with FoG severity (Schlenstedt et al., 2016). Reduced LoS outcomes could be associated with fear of falling and in freezers probably revealed learned behavior to cope with an awareness of instability, but could also be influenced by range of motion and muscle strength. As such, deficits in this domain may not reflect a primary pathway to explain FoG and postural instability.

3.1.3 Sensory reweighting

Table 2 additionally presents how disturbing sensory input during stance affects postural control differently between freezers and non-freezers. The large and well-matched study of Huh et al. (2016), using the sensory organization test (SOT) in the OFF-state, found that restricting visual information and manipulating somatosensory input resulted in poorer postural control in freezers compared to non-freezers, as apparent from lower equilibrium scores (Huh et al., 2016). In contrast, using the same SOT test in a small population of patients with and without FoG in the ON-state, Vervoort et al. (2013) found no differences in postural control when either visual or somatosensory input was eliminated, but only

when both visual and proprioceptive information were distorted (Vervoort et al., 2013). In this condition, non-freezers showed more hip strategy, whereas freezers and controls used more ankle strategy to maintain balance. As in both studies, groups were well-matched, these discrepant results may be explained by medication state (Table 1). Poorer postural control was also found in freezers compared to non-freezers during ON-medication when proprioceptive, but not when visual information was disturbed (Ehgoetz Martens et al., 2016). Inconsistent results pertaining to the manipulation of visual information, sometimes suggested an increased reliance on vision in freezers and sometimes not (Kim et al., 2016; Pelykh et al., 2015). However, longer disease progression or duration, present in 3 out of 5 studies, may have confounded these results. Overall, there seems to be a different reweighting of sensory input between groups.

3.2. FoG and reactive postural control

The question of whether reactive postural control is affected differently in freezers compared to non-freezers elicited conflicting results in different studies (**Table 3**). Freezers were shown to have slower and smaller corrective stepping responses compared to non-freezers (Smulders et al., 2014; Sutter et al., 2017), whereas other studies reported that reactive postural control was similar between freezer and non-freezers (Nonnekes et al., 2015; Peterson and Horak, 2016), or even better in freezers (Vervoort et al., 2013). The study with the largest population reported more impaired compensatory stepping in freezers, but the higher disease severity in this group and lack of standardized measurement compromised the freezing-specificity of the findings (Sutter et al., 2017). Inconsistent results were also specific to the direction of the platform translations. Interestingly, the effect of providing a startling auditory stimulus to accelerate postural responses was attenuated in freezers compared to non-freezers (Nonnekes et al., 2015). This result is particularly noteworthy as startling reactions are thought to be mediated by the pedunculopontine (PPN) and the pontomedullary reticular formation (pmRF) (Nonnekes et al., 2015; Nonnekes et al., 2014a; Thevathasan et al., 2011), areas which were also suggested to be involved in FoG (Fling et al., 2013; Schweder et al., 2010; Thevathasan et al., 2011). Also, flexible switching between postural strategies (i.e. step or feet-in-place response) to overcome balance perturbations of various amplitudes was similar between freezers, non-freezers and healthy controls (Smulders et al.,

2014). The ability to improve and retain benefits on protective postural response after repetitive surface perturbations and training, was reduced in freezers, regardless of medication state (Peterson and Horak, 2016; Smulders et al., 2014). These two studies underscored a reduced implicit motor learning ability of reactive postural control in freezers. Finally, balance control in response to perturbations was found to be asymmetrical in about 75% of PD patients, but this was not more pronounced in freezers (Boonstra et al., 2014). In sum, reactive postural control parameters are slower and smaller in size but otherwise largely preserved in patients with freezing, with the exception of those elicited by startle. The evidence provided by studies with groups of similar disease severity and cognitive abilities seems robust enough to conclude that reactive postural instability appears to be not more affected in freezers, suggesting a separate mechanism.

3.3. FoG and anticipatory postural adjustments

Table 4 summarizes studies investigating APAs prior to self-triggered or cued gait initiation in freezers and non-freezers. As stated previously, FoG may reflect a decoupling problem between the postural preparation phase and the stepping. However, this hypothesis stems from a balance perturbation paradigm and not, such as reviewed here, by evidence from studies assessing self-initiated stepping. Three out of 8 studies reported smaller APA amplitudes with a longer duration in freezers compared to non-freezers (Beaulne-Seguin and Nantel, 2016; Delval et al., 2014; Tard et al., 2014). More specifically, the time between the backward CoP shift and toe-off was longer, the maximum AP and/or ML CoP shift was smaller and sometimes APAs were absent altogether in freezers or involved multiple inappropriate APAs (Beaulne-Seguin and Nantel, 2016; Delval et al., 2014; Tard et al., 2014). Multiple APAs increased forward CoM motion, but less so in freezers compared to non-freezers (Cohen et al., 2017). Small APAs may thus point to inadequate scaling of the weight shift needed to initiate stepping or a protective strategy to reduce postural demand. However, APA amplitude and onset were only different in freezers compared to non-freezers in the presence of an auditory or a visual cue prior to gait initiation (Beaulne-Seguin and Nantel, 2016; Delval et al., 2014; Nonnekes et al., 2014a; Tard et al., 2014). Interestingly, when using an imperative auditory startling stimulus, similar acceleration of APA-behavior was found in freezers, non-freezers and controls, although somewhat attenuated in freezers

(Nonnekes et al., 2014a). Yet, reactive stepping in response to a perturbation was affected (Cohen et al., 2017; Delval et al., 2014; Nonnekes et al., 2014a). Thus, the hypokinetic APAs may not only signify an inefficient uncoupling of the CoP and CoM (Hass et al., 2005), but also reduce the force production of the swing limb. Others proposed that APA abnormalities could be explained by proprioceptive deficits as a result of a reduced responsiveness to loading and unloading in PD (Dietz and Duysens, 2000; Mensink et al., 2014). Proprioceptive deficits were found to be present in patients with PD, contributing to their postural deficits (Carpenter and Bloem, 2011). However, Mensink et al. showed that APAs were not affected by manipulating sensory input in a freezing cohort (not included in table 4, as no comparison was made between freezers and non-freezers). Recent research demonstrated no substantial differences in APAs between freezers and non-freezers while ON or OFF medication nor when adding a cognitive loading (Bonora et al., 2017; Cohen et al., 2017; de Souza Fortalez et al., 2017; Plate et al., 2016). Similarly, no differences in APAs between groups were found in OFF-trials without startling reactions (Nonnekes et al., 2014a) or in the ON-state without presenting a conflicting visual or auditory cue prior to gait initiation (Beaulne-Seguin and Nantel, 2016; Delval et al., 2014; Tard et al., 2014). In addition, anticipatory weight shifts prior to a single-leg balance task, instead of gait initiation, also showed no differences between freezers and non-freezers (Bonora et al., 2017).

In sum, as 5 out of 8 studies showed abnormalities in APAs and step onsets in freezers upon imperative stimuli compared to non-freezers, we propose that under time-constraints, freezers generate abnormal APAs because of an inability to quickly inhibit an ongoing motor program, or alternatively, to activate a preparatory motor program. On the other hand, cues reduced the number of multiple APAs and absences of APAs in freezers compared to self-initiated gait initiation (Delval et al., 2014) and may thus substitute the disordered automatic release of the preparatory response. Taken together, APAs in freezers are characterized by smaller CoP amplitudes, longer duration, a delayed onset and less directional control. A remaining question is whether APA-dysregulation reflects a primary mechanism underlying FoG or a secondary compensatory mechanism to overcome the akinetic state, especially when multiple but ineffective APAs are generated.

3.4. FoG and dynamic postural control

3.4.2. FoG and stepping in place

Inappropriate APAs prior to gait initiation also point towards freezing-related weight-shifting impairments, reflecting an associated disturbance of dynamic postural control. **Table 5** demonstrates that stepping in place (continuous weight-shifting) was disturbed in patients with FoG in all studies, as shown by more asymmetric and dysrhythmic force plate signals (Killane et al., 2015; Nantel and Bronte-Stewart, 2014; Nantel et al., 2011; Nantel et al., 2012). Rhythmicity and symmetry also differed significantly between freezers and non-freezers both ON and OFF medication. Medication did not induce changes of these metrics, but reduced the occurrence of freezing episodes during this task (Nantel and Bronte-Stewart, 2014). Hence, it seemed that FoG itself responded to dopaminergic medication, but the underlying postural control mechanism was less responsive, suggesting more involvement of non-dopaminergic pathways in the latter. Freezers had higher UPDRS-III scores and/or a longer disease duration in 3 out of 4 of these studies, showing that disease severity may have confounded the findings. In addition, cognitive measures were worse in freezers or unreported, for which cognition cannot be excluded as a modifying factor in this domain. Along the same lines, training of stepping in place on a balance board with cognitive loading was shown to improve symmetry and rhythmicity and reduced the number of FoG episodes (Killane et al., 2015). In sum, the differences observed in parameters of stepping in place by freezers compared to non-freezers mimic the behavioral pattern found prior to a FoG episode in which freezers show reduced step sizes, rhythmicity and symmetry of the gait cycles (Chee et al., 2009). This similarity may imply a partial common neurological pathway between dynamic postural control (as operationalized by assessing weight-shifting in stepping in place) and FoG.

3.4.3. FoG and turning

Table 5 also illustrates studies which investigated postural components of 180-degree turns in patients with and without FoG. Two of those studies showed that turning in freezers was characterized by a closer coupling between the head and pelvis and a delay in head rotation, indicating reduced trunk movement during turning (McNeely and Earhart, 2011; Spildooren et al., 2013). Two other studies found step width decreases in patients with FoG in both ON and OFF (Bengevoord et al., 2016; Bhatt et al.,

2013). Specifically, prior to a freezing episode, the CoM position was found to be less medially and more forwardly oriented and step width became narrower compared to turning sections without freezing (Bengevoord et al., 2016). However, no overall group differences between freezers and non-freezers in CoM behavior during normal turning were found. Of note, the segmental inflexibility and smaller step widths were most pronounced at the end of the turn when FoG episodes most frequently occurred (Bhatt et al., 2013; Spildooren et al., 2013). These findings confirm that dynamic postural control is affected and leads to delayed postural preparation for the change in spatial orientation during the turn. The smaller step widths could be inherent to underscaled weight-shifting ability. Decreased step widths prior to the FoG episodes narrows the base of support, which likely contributes and forms the antecedents of FoG and instability during turning. As the abovementioned turning problems occurred in both ON and OFF medication and were present in well-matched groups, we conclude that these results suggest a close connection between dynamic postural control and FoG.

4. DISCUSSION

This review summarized posturography studies that compared freezers and non-freezers to investigate the strength and nature of the connection between different aspects of postural instability and FoG. We found that freezing-related postural instability cannot be attributed to one specific deficit of postural control, as the various systems showed to a greater and lesser extent differences between subgroups. However, based on the evidence so far, the largest differences between freezers and non-freezers were apparent in dynamic postural control and anticipatory postural adjustments. Less evidence supported difficulties during quiet stance and reactive postural control. In the sections below, these findings will be related to the espoused models of the relationship between FoG and postural instability as put forward in the introduction.

4.1. The independent model

Some insights based on the review of the literature above appear to support the idea that FoG and postural instability are two independent phenomena. The high number of non-significant outcomes

across all 27 studies taken under consideration underscore that no specific postural control parameter assessed consistently differentiates freezers from non-freezers. This may indicate that postural instability and FoG are two independent phenomena or that posturographic data and protocols are still very variable, difficult to interpret or not sensitive enough. Recently it was shown, that APA's are also frequently absent in, or differ between, healthy people (Lu et al., 2017). This suggests that postural strategies for gait initiation are highly individual, depend on the postural strategy and are not necessarily related to FoG.

Supporting a degree of independence is that dopaminergic medication reduced the occurrence of FoG, but did not influence weight-shifting and decreased balance performance under sensory constraints (Ehgoetz Martens et al., 2016; Nantel and Bronte-Stewart, 2014). This suggests that the involvement of non-dopaminergic pathways is more pronounced in postural instability than in FoG. On the contrary, weight-shifting practice improved stepping in place and FoG (Killane et al., 2015). By and large, as will be discussed in the next sections, results revealed only partial independence.

4.2. The consequence model

The combined literature on differences between freezers and non-freezers link postural control and FoG in a bidirectional manner and as such assume a behavioral relationship in line with model II (Figure 1), although a truly behavioral aftereffect of one over the other was not studied until now. However, the motor abnormalities inherent to postural instability and FoG can be reasoned to exacerbate the phenomena in a bidirectional fashion. The unstable posture due to a narrowed base of support in freezers compared to non-freezers found during turning in this review, (Bengevoord et al., 2016; Bhatt et al., 2013) may create instability and trigger FoG as it impedes the base of support for unloading the swing limb and generating APAs. Equally, a more posterior CoP position during quiet stance in freezers, may reduce the amount of force and velocity which needs to be generated throughout the gait initiation phase and causing gait initiation problems (Schlenstedt et al., 2016). Increased hip and knee flexion and an anterior tilted pelvis (i.e. stooped posture) was shown prior to a FoG episode (Nieuwboer et al., 2007). A stooped position hampers the generation of a large forward momentum by the trunk. These abnormalities together may biomechanically explain the increased propensity for backward postural

instability and falling in freezers and for gait initiation difficulties. Components of FoG and postural instability could thus mutually reinforce each other, without it being clear what is the cause and what is the effect?

4.3. The overlap model

Disease progression and medication have a differential influence on postural control outcomes (Curtze et al., 2015) and FoG. This review showed that Unified Parkinson's Disease Rating Scale part III (UPDRS III) scores, H&Y stages and/or LED were not consistently reported or well-matched between freezer and non-freezer groups. When reported, freezers frequently had a longer disease duration, higher UPDRS-III scores, higher H&Y stage and a higher LED. What is unknown is how the underlying pathology of each phenomenon progresses and whether this is interlinked. Recently, it was shown that patients with more severe decline of postural instability were more likely to develop FoG (Vervoort et al., 2016). Findings from DBS studies strengthen a partial overlap of pathophysiology. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) was shown to reduce FoG (Moreau et al., 2008; Vercruysse et al., 2014b), and to improve reactive postural control and quiet standing through enhancing processing of sensory information. However, STN-DBS had no or a deteriorating effect on dynamic postural control, in particular on APAs (Collomb-Clerc and Welter, 2015). PPN-DBS on the other hand, tended to improve APAs, falls and FoG (Collomb-Clerc and Welter, 2015; Morita et al., 2014), although the results of a recent meta-analysis showed data to the contrary (Golestanirad et al., 2016). Although data are still inconsistent, some evidence points in the direction that FoG and postural control can deteriorate and improve synergistically, depending on the specific pathways targeted. Thus, it cannot be ruled out that FoG and postural instability have, at least to a certain extent, common disturbances of the underlying neural circuitry.

4.4. Which components of postural instability are most involved in FOG?

In Figure 2 we provide a graphical representation of the possible FoG -postural control interactions and their modulatory effects, based on the results of the studies considered in this review. **Figure 2**, panel A shows that the greatest freezing-related postural difficulties (dynamic postural control and APA's) could

be explained by motor timing deficits and reduced flexibility to shift between motor strategies (Mohammadi et al., 2015; Smulders et al., 2015), contributing to inefficient uncoupling of the CoP and CoM in preparation for forward progression. Alternatively, this impaired uncoupling possibly also reflects a protective strategy to reduce the postural demand on preparatory movement. In both cases, dysfunctional uncoupling results in hypokinetic weight shifts, and reduced force production for unloading, impacting on the release of a postural response (**Figure 2**, panel A). This explains why in the face of imperative stimuli and time-constraints, freezers were unable to release a motor program, expressed as smaller weight shifts, steps widths and lengths, longer movement durations and under-scaled balance corrections compared to their non-freezing counterparts. This proposed inability to suppress ongoing motor programs or to activate a new ones is likely mediated by altered prefrontal activity, known to be altered in freezers (Fling et al., 2013; Shine et al., 2013; Vercruysse et al., 2014a). As for other neurological origins, deficits of dynamic postural control and APA-regulation point towards involvement of the supplementary motor area (SMA) and the premotor area, which not surprisingly were also found to be associated with FoG (Collomb-Clerc and Welter, 2015; Ferraye et al., 2014; Jacobs et al., 2009a; Takakusaki, 2017). Another important region involved in preparatory postural control is the mesencephalic locomotor region (MLR), a brain area connected to the SMA and also strongly implicated in FoG (Ferraye et al., 2014; Fling et al., 2014; Snijders et al., 2016). Reduced connectivity between the PPN and SMA was recently shown to be associated with increased APA duration (Gallea et al., 2017). As PPN-DBS improved CoP velocity and APA-amplitude, but not duration (Collomb-Clerc and Welter, 2015). This could indicate that the true deficit underlying FoG is not primarily postural but rather a preparatory problem with the generation of stepping itself. Furthermore, animal studies showed that the ventral part of the MLR serves the postural regulation of upright stance, whereas the dorsal part of the MLR is controlling movement rhythmicity and locomotion (Sherman et al., 2015), supporting a segregated role. Hence, the latter part is likely to be implicated in APAs and dynamic control. Lesions of the dorsal MLR resulted in akinesia as shown in animal models (Sherman et al., 2015). Furthermore, findings based on motor imagery suggest that the latero-rostral part of the MLR might regulate balance, whereas the medial-caudal MLR is involved in gait (Ferraye et al., 2014). The effectors of balance and gait, primarily concerning the trunk and legs, are also assumed to

have different somatotopic representations in various brain regions (Ferraye et al., 2014; Preuss et al., 1996). Hence, depending on the affected regions, deficits may occur which rely more or less on trunk or leg control.

[Insert Figure 2]

Figure 2, panel B shows that impaired sensory reweighting, retropulsive CoP positioning and decreased limits of stability can all exacerbate postural instability, although our findings showed only modest links with FoG. Proprioceptive perturbations during quiet stance were more affected in freezers, but whether this is due to compensatory behavior, more pronounced sensory disintegration or worse disease profiles was not clarified. The basal ganglia and cerebellum have an important complementary role in processing and integrating sensory input for postural control (Doya, 2000). Whereas the basal ganglia serve the regulation of muscle tone and coordination, the cerebellum is an important neural structure for error-corrections of the internal model of upright stance. Recent work showed that the locations of brain lesions associated with FoG were functionally connected to the dorsal medial cerebellum (Fasano et al., 2017). In contrast, applying cerebellar theta burst stimulation did not affect FoG (Janssen et al., 2017). Cerebellar involvement may have a mediating role on postural control and FoG (Fasano et al., 2017; Takakusaki, 2017), thereby influencing the postural control mechanisms depicted in panel 2A indirectly. Interestingly, we found that the most automatic mechanism of postural stability, i.e. reactive postural control, was probably least involved in FoG. This coincides with the earlier finding that dual tasking during platform perturbations was shown to increase the incidence of falls without affecting the occurrence of FoG (Jacobs et al., 2014). The release of automatic postural responses is also presumed to involve brainstem structures. Possibly, due to the earlier discussed spatial segregation of the MLR, automatic responses arise from both preparatory and releasing neural circuits within the brainstem (Nonnekes et al., 2015). These findings explain that when patients have to rely even more strongly on automatic reactive processing, FoG and postural control may be steered by separate mechanisms, while when depending on slower preparatory processing the mechanisms might be similar.

4.5. Future recommendations & clinical implications

Our methodological analysis in this review showed that contradictory evidence on the link between FoG and postural control can be attributed to differences in sample size, tests used to classify freezers and non-freezers, and group differences in disease severity and medication state. The many different posturographic methods, the large number of parameters extracted and the variable outcomes stress the need for power-based studies in this field. In order to generate new and more solid insights, postural control should be assessed by means of standardized tests and parameters. For this purpose, we propose to focus on balance assessments with one common primary outcome measure to quantify postural stability, allowing comparisons between studies. As linear measures of CoP and CoM are subject to body metrics, such as body height and base of support, we recommend to evaluate postural control using parameters describing CoM and CoP coordination, as well as variability measures to describe stability in both static and dynamic situations (Bruijn et al., 2013). Detailed kinematics should be combined with explanatory variables, such as EMG assessments, to further understand the neuromuscular control in patients with FoG.

The diversity of the behavioral findings captured in this review are in accordance with neuroimaging studies showing that freezing implicates various nodes in a wide network (Lewis and Shine, 2016). Also, identifying FoG subtypes should receive more attention to further tailor rehabilitation strategies and medical treatment to these specific impairments. The precise neural circuitries that contribute to the pathophysiology of FoG and postural instability need to be unraveled via more sensitive brain imaging methods (e.g. 7 Tesla MRI), allowing the visualization of brainstem regions with sufficient density. Lastly, longitudinal approaches are needed to determine whether the emergence of postural instability and FoG are causally linked.

Finally, this review raises the possibility that FoG arises from a postural ‘biomechanical’ deficit as well as from a neurological inability to release motor output. Training of these postural components may be able to ameliorate FoG (Killane et al., 2015). Particularly, the poor timing of postural changes points towards a potential freezing-specific training target. However, the reduced postural motor learning ability as applied to reactive postural control, found in freezers, (Peterson and Horak, 2016; Smulders et al., 2014) would argue against this possibility. Based on this review, it is not recommended to train reactive postural control but rather tackle the timing and flexibility during dynamic and anticipatory

postural adjustments to ameliorate freezing-related postural instability. Future work is needed to examine whether training interventions targeting both FoG and postural instability will have extra clinical benefits on fall frequency and FoG.

CONCLUSION

This review showed that freezers have greater weight-shifting impairments, delayed movement onset, reduced acceleration and increased duration of postural corrections during dynamic postural control tasks and anticipatory postural adjustments compared to non-freezers. Postural impairments became most apparent in situations requiring fast motor planning and adjustment to a changing context. Furthermore, it seems that postural instability is behaviorally reinforced and exacerbated by FoG and vice versa. An incremental influence of several postural deficits could generate a vicious circle of postural breakdown, which manifest itself stronger in freezers than in non-freezers. This negative cycle of combined postural deficits, resembles a similar pattern of gait-break down leading to FoG. Intervention studies which address both components are needed to further unravel the overlay of postural instability and FoG.

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Conflict of Interest Statement

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Figure Captions

Figure 1. Models of the relationship between postural instability and FoG.

Model I – the independent model, describes postural instability and freezing are two independent phenomena, not sharing common neural mechanisms and no causal relationship is existing. In model II – the consequence model, postural instability and freezing are presented as two independent phenomena. Increased postural instability is a consequence of the underlying pathophysiology of FoG, or FoG is a consequence of postural instability. Model III – the overlap model, displays postural instability and freezing are partially overlapping phenomena and co-occur. Increased postural instability is a consequence of a common underlying pathophysiology that also contributes to FoG.

Figure 2. Components of freezing-related postural instability.

The black arrows in panel A show that the release of a pre-programmed motor program may result in normal postural responses across all domains in patients with FoG. The red arrows indicate that poor timing and inflexibility of switching between motor programs could disorder the release of postural responses in people with FoG. The dotted arrows in panel B delineate the modulating influence of the sensory system operating as a continuous control system. Major changes in sensory input require a reweighting of the available sensory resources, which might be different in FoG and impede integration processes. Panel C indicates that neural overlap between postural instability and FoG is likely in brain areas responsible for the regulation of movement preparation, timing and coordination. Colored bars show the strength of the evidence for freezing-related postural instability (% of number of studies), determined by two independent raters.

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Table 1. Characteristics of the studies

Studies included	Groups	Criterion FoG	FoG classification method	ON/OFF	Disease differences	Cognitive differences	Medication differences (LED)	Age
(Bhatt et al., 2013)	N = 10 FR N = 10 NFR	Self-reported/objectively verified	Patients self-reported FoG, FoG-provoking tests	ON	UPDRS III = DD - H&Y -	-	-	=
(Beaulne-Seguín and Nantel, 2016)	N = 12 FR N = 13 NFR	Self-reported	FOG-Q item 3	ON	UPDRS III > DD = H&Y -	MoCA =	-	=
(Bengevoord et al., 2016)	N = 16 FR N = 14 NFR	Self-reported	NFOG-Q item 1	OFF	UPDRS III = DD = H&Y =	MMSE <	LED =	=
(Bonora et al., 2017)	N = 25 FR N = 33 NFR	-	-	OFF	UPDRS III > DD - H&Y >	-	-	=
(Boonstra et al., 2014)	N = 9 FR N = 11 NFR	Self-reported/objectively verified	NFOG-Q, FoG-provoking tests	OFF	UPDRS III = DD = H&Y =	FAB =	-	=
(Cohen et al., 2017)	N = 12 FR N = 13 NFR	Self-reported	-	OFF	UPDRS III > DD = H&Y >	-	-	=
(Delval et al., 2014)	N = 30 FR N = 30 NFR	Self-reported/objectively verified	FOG-Q item 3, FoG-provoking tests	ON	UPDRS III - DD > H&Y -	MMSE -	-	=
(Ehgoetz Martens et al., 2016)	N = 14 FR N = 17 NFR	Self-reported/objectively verified	Patients self-reported FOG, observation	ON/OFF	UPDRS III > DD - H&Y -	3MS =	LED =	=
(Huh et al., 2016)	N = 25 FR N = 22 NFR	Objectively verified	NFOG-Q item 1, FoG-provoking tests	OFF	UPDRS III = DD = H&Y =	MoCA = FAB =	LED =	=
(Killane et al., 2015)	N = 13 FR N = 7 NFR	Self-reported	NFOG-Q	ON	UPDRS III > DD - H&Y =	MoCA < FAB <	LED =	=
(Kim et al., 2016)	N = 17 FR N = 19 NFR	Self-reported	NFOG-Q	OFF	UPDRS III = DD > H&Y =	K-MMSE =	-	=
(McNeely and Earhart, 2011)	N = 10 FR N = 10 NFR	Self-reported	FOG-Q item 3	ON/OFF	UPDRS III = DD = H&Y -	-	LED >	=
(Nantel and Bronte-Stewart, 2014)	N = 15 FR N = 15 NFR	Self-reported, objectively verified	FOG-Q item 3, SIP	ON/OFF	UPDRS III > DD > # H&Y -	-	-	=
(Nantel et al., 2011)	N = 15 FR N = 15 NFR	Self-reported	FOG-Q item 3	OFF	UPDRS III = DD - H&Y -	-	-	=
(Nantel et al., 2012)	N = 18 FR N = 11 NFR	Objectively verified	FOG-Q item 3, SIP task	OFF	UPDRS III = DD > H&Y -	Visuospatial domains < Executive function =	-	=
(Nonnekes et al., 2014a)	N = 12 FR N = 14 NFR	Objectively verified	NFOG-Q, FoG-provoking tests	OFF	UPDRS III = DD > H&Y -	FAB =	-	=
(Nonnekes et al., 2015)	N = 11 FR N = 14 NFR	Objectively verified	NFOG-Q, FoG-provoking tests	End of dose	UPDRS III = DD - H&Y -	FAB =	-	=

(Pelykh et al., 2015)	N = 15 FR N = 17 NFR	Self-reported	FOG-Q item 3	ON	UPDRS III - DD > # H&Y > #	-	-	=
Peterson & Horak, 2016	N = 13 FR N = 15 NFR	Self-reported	NFOG-Q	ON	UPDRS III = DD > H&Y -	MoCA =	LED =	=
(Plate et al., 2016)	N = 16 FR N = 10 NFR	Self-reported	FOG-Q item 3/ FOG-Q >7	ON	UPDRS III = DD = H&Y =	-	LED >	=
Schlenstedt et al., 2015	N = 31 FR N = 27 NFR	Probable/self-reported	FOG-Q item 3	ON	UPDRS III = DD = H&Y =	-	-	=
(Smulders et al., 2014)	N = 14 FR N = 14 NFR	Self-reported	NFOG-Q	OFF	UPDRS III = DD - H&Y =	MMSE =	-	=
(Spildooren et al., 2013)	N = 13 FR N = 14 NFR	Self-reported	NFOG-Q item 1	OFF	UPDRS III = DD = H&Y =	MMSE =	-	=
(de Souza Fortaleza et al., 2017)	N = 24 FR N = 30 NFR	Self-reported	NFOG-Q item 1	OFF	UPDRS III = DD = H&Y -	MoCA =	LED =	=
(Sutter et al., 2017)	N = 46 FR N = 65 NFR	Self-reported	NFOG-Q item 1	OFF	UPDRS III > DD > H&Y >	-	-	=
(Tard et al., 2014)	N = 15 FR N = 15 NFR	Self-reported/ objectively verified	FOG-Q item 3, FoG-provoking tests	ON	UPDRS III = DD > H&Y -	MMSE = FAB =	LED >	=
(Vervoort et al., 2013)	N = 9 FR N = 10 NFR	Self-reported	FOG-Q item 3	ON	UPDRS III = DD = H&Y =	MMSE =	LED =	=

Analysis statistically accounted for confounders.

Not reported or significance not reported (-); no significant differences between FR and NFR (=); significantly higher in FR compared to NFR (>); significantly lower in FR compared to NFR (<).

3MS, modified MMSE; FAB, Frontal Assessment Battery; FOG-Q, Freezing of Gait Questionnaire; FR, freezers; LED, levodopa equivalent dose; DD, disease duration; H&Y, Hoehn and Yahr stage; NFOG-Q, K-MMSE, Korean MMSE; New Freezing of Gait Questionnaire; NFR, non-freezers; MMSE, Mini-Mental State Examination; SCOPA-COG, cognitive section of the Scales for Outcomes in PD; sUPDRSm, short UPDRS motor scale; UPDRS-III, Unified Parkinson's Disease Rating Scale part III (motor examination). Self-reported, FoG reported by patient; objectively verified, FoG observed by examiner; probable, FoG reported by caregiver.

Table 2 – Quiet stance

Studies included	Sample size	ON/OFF	Task paradigm	Main findings, differences FR-NFR	Main non-significant outcomes
(Vervoort et al., 2013)	N = 9 FR N = 10 NFR	ON	Quiet standing EO (SOT 1)	-	ES SOT 1
(Nantel and Bronte-Stewart, 2014)	N = 15 FR N = 15 NFR	OFF	Quiet standing EO	-	CoP (AP, ML): RMS amplitude, mean velocity
(Pelykh et al., 2015)	N = 15 FR N = 17 NFR	ON	Quiet standing EO	-	CoP: sway path length, normalized sway path length, sample entropy, radius
(Schlenstedt et al., 2016)	N = 31 FR N = 27 NFR	ON	Quiet standing EO	Average CoP position AP more posterior in FR	CoP (AP, ML): RMS amplitude, mean velocity, sample entropy, postural symmetry indices
(Ehgoetz Martens et al., 2016)	N = 14 FR N = 17 NFR (OFF)	ON+OFF	Quiet standing EO	-	CoG sway index
(Huh et al., 2016)	N = 25 FR N = 22 NFR	OFF	Quiet standing EO (SOT 1)	-	ES SOT 1
(Kim et al., 2016)	N = 17 FR N = 19 NFR	OFF	Quiet standing EO	AP CoP range ↑ in FR AP CoP position ↑ in FR AP ellipse area ↑ in FR AP RMS ↑ in FR	CoP (AP, ML): velocity, RMS distance, total power frequency, edge frequency, Lyapunov exponent, ML range, 95% confidence ellipse, AP CoP position ML RMS, ML JERK, AP, JERK. No DT-effect
(de Souza Fortaleza et al., 2017)	N = 24 FR N = 30 NFR	OFF	Quiet standing EO, with and without cognitive DT		
Limits of stability (Schlenstedt et al., 2016)	N = 31 FR N = 27 NFR	ON	Maximal voluntary leaning	Maximal AP CoP displacement ↓ in FR; CoP forward movement ↓ in FR	LoS average distance and posterior CoP position
Sensory reweighting (Vervoort et al., 2013)	N = 9 FR N = 10 NFR	ON	SOT	FR ankle strategy ↑ (EC + proprioception #) NFR hip strategy ↑ (EC + proprioception #)	ES SOT 1-6, postural strategy SOT 1-5
(Pelykh et al., 2015)	N = 15 FR N = 17 NFR	ON	Quiet standing EC and EC + DT	Radius of CoP trajectory EC ↑ in FR	CoP: sway path length, normalized sway path length, sample entropy, radius (DT)
(Ehgoetz Martens et al., 2016)	N = 14 FR N = 17 NFR (OFF)	ON+OFF	Clinical Test of Sensory Interaction on Balance	CoG sway ↑ in FR, ON-medication (EO + proprioception #)	CoG sway index firm and foam surface EC
(Huh et al., 2016)	N = 8 FR N = 16 NFR N = 25 FR N = 22 NFR	OFF	SOT	ES ↓ in FR* (EC + proprioception # (SOT 4-5-6)); Sensory ratios: FR ↓ visual and vestibular processing	ES SOT 1-2-3, SR-SOM, SR-VISPREF
(Kim et al., 2016)	N = 17 FR N = 19 NFR	OFF	Quiet standing EC	-	CoP (AP, ML): velocity, RMS amplitude, total power frequency, edge frequency, Lyapunov exponent, range, 95% confidence ellipse, AP CoP position

Note: AP, anterior-posterior; CoG, center of gravity; CoP, center of pressure; DT, dual-task; EC, eyes closed; EO, eyes open; ES, equilibrium score (maximum angle of CoG sway over the theoretical LoS); FR, freezers; LoS, limits of stability; ML, medial-lateral; NFR, non-freezers; RMS, root mean square; SOT, sensory organization test; SR, sensory ratio (contribution of sensory input to postural control); SR-SOM/VIS/VEST, ability to use somatosensory/visual/vestibular information; SR-VISPREF, dependency on visual information; SR-MANSOM, ability to manage distorted somatosensory inputs.

indicates disturbance of sensory input; *Lower score indicates poorer balance control

Table 3 – Reactive postural control

Studies included	Sample size	ON/OFF	Task paradigm	Main findings, differences FR-NFR	Main non-significant outcomes
(Vervoort et al., 2013)	<i>N</i> = 9 FR <i>N</i> = 10 NFR	ON	FW + BW platform translations, different magnitudes	BW, medium size: Response strength* ↓ in FR	Response strength (FW and BW)
(Smulders et al., 2014)	<i>N</i> = 14 FR <i>N</i> = 14 NFR	OFF	FW platform translations, different magnitudes	Step lengths ↓ in FR Leg angles ↓ in FR	Step onset, trunk angle, number of steps, postural set switching effect
(Boonstra et al., 2014)	<i>N</i> = 9 FR <i>N</i> = 11 NFR	OFF	Continuous platform movements and force perturbations at the sacrum in sagittal plane	-	Weight-bearing % and R-L asymmetry ankle and hip joint
(Nonnekens et al., 2015)	<i>N</i> = 11 FR <i>N</i> = 14 NFR	OFF	FW platform translations, accompanied by a SAS in 25% of trials	<i>Without SAS:</i> - <i>With SAS:</i> Accelerated onset TA+RF ↓ in FR Step onset latency ↑ in FR	Without SAS: Onset latency, amplitude TA+RF, With + without SAS: step onset, step length, leg angle, number of steps
(Peterson and Horak, 2016)	<i>N</i> = 13 FR <i>N</i> = 15 NFR	ON	Platform translation in FW + BW direction	<i>Baseline (day 1)</i> - <i>Training (after day 1)</i> FW: Improvement in CoM displacement ↓ in FR <i>Retention (day 2)</i> FW: CoM displacement retention effect ↓ in FR Velocity + step length (FW+BW)	CoM displacement (BW), margin of stability, first step latency and length, number of steps
(Sutter et al., 2017)	<i>N</i> = 46 FR <i>N</i> = 65 NFR	OFF	FW + BW leaning (Mini-BEST item 4+5)	-	-

Note: BW, backward; CoM, center of mass; FR, freezers; FW, forward; RF, Rectus Femoris; SAS, startling auditory stimulus; TA, Tibialis Anterior.

* Low response strength indicates adequate amplitude scaling

Table 4 – Anticipatory postural control

Studies included	Sample size	ON/OFF	Task paradigm	Main findings, differences FR-NFR	Main non-significant outcomes
(Delval et al., 2014)	<i>N</i> = 30 FR <i>N</i> = 30 NFR	ON	First-step preparation and execution under self-triggered and cued conditions	APA amplitude, AP ↓ in FR (<i>cued</i>) APA duration ↑ in FR (<i>cued</i>) APA onset ↑ in FR (<i>cued</i>)	Number, ML amplitude (<i>cued</i>), AP + ML amplitude, duration (self-triggered)
(Tard et al., 2014)	<i>N</i> = 15 FR <i>N</i> = 15 NFR	ON	GI, with and without attentional load	Number of inappropriate APAs ↑ in FR APA amplitude, AP ↓ in FR (<i>visual cue</i>) APA amplitude, ML ↓ in FR (<i>visual cue</i>) APA amplitude, ML ↓ in FR (<i>auditory cue</i>) APA duration ↑ in FR (<i>auditory cue</i>) APA onset ↑ in FR (<i>auditory cue</i>)	APA onset and duration (<i>visual cue</i>), ML amplitude (<i>auditory cue</i>)
(Nonnekkes et al., 2014a)	<i>N</i> = 12 FR <i>N</i> = 14 NFR	OFF	Rapid GI task with a SAS in 25% of trials	Accelerated APA onset ↓ in FR (<i>SAS</i>)	APA amplitude (with and without SAS), onset (without SAS), number
(Beaulne-Seguin and Nantel, 2016)	<i>N</i> = 12 FR <i>N</i> = 13 NFR	ON	GI and inhibition, following conflicting and non-conflicting visual cues	APA amplitude, AP ↓ in FR (<i>GI, conflicting cues</i>) APA duration ↑ in FR (<i>GI, conflicting cues</i>)	<i>Gait initiation, conflicting cues</i> APA velocity (AP, ML), amplitude (ML) <i>Gait initiation, non-conflicting cues</i> APA velocity, amplitude, duration <i>Gait inhibition</i> RMSCoP (AP, ML), VCoP (AP, ML)
(Plate et al., 2016)	<i>N</i> = 16 FR <i>N</i> = 10 NFR	ON	GI, self-paced and externally cued	Step latency ↑ in FR (<i>cued</i>)	APA amplitude (AP, ML), APA duration, number
(de Souza Fortaleza et al., 2017)	<i>N</i> = 24 FR <i>N</i> = 30 NFR	OFF	GI, with and without cognitive DT	-	APA peak (ML, AP), APA duration
Bonora 2017	<i>N</i> = 25 FR <i>N</i> = 33 NFR	OFF	One-Leg Stance test	-	ML peak trunk acceleration, time to peak, peak to balance, nRMS acceleration
Cohen 2017	<i>N</i> = 12 FR <i>N</i> = 13 NFR	OFF	GI, simple and choice cued conditions	Forward CoM motion ↓ in FR during multiple vs single APAs (Similar to HC)	Number, APA onset, duration, step onset, CoM AP position

Note: AP, anterior-posterior; APA, anticipatory postural adjustment; CoG, center of gravity; CoP, center of pressure; DT, dual-task; FR, freezers; GI, gait initiation; ML, medio-lateral; NFR, non-freezers; nRMS; RoM, range of motion; SAS, startling auditory stimulus; ST, self-triggered.

Table 5 – Dynamic postural control

Studies included	Sample size	ON/OFF	Task paradigm	Main findings, differences FR-NFR	Main non-significant outcomes
Stepping in place					
(Nantel et al., 2011)	<i>N</i> = 15 FR <i>N</i> = 15 NFR	OFF	SIP task	SIP asymmetry ↑ in FR SIP arrhythmicity ↑ in FR	Mean stride duration
(Nantel et al., 2012)	<i>N</i> = 18 FR <i>N</i> = 11 NFR	OFF	SIP task	SIP asymmetry ↑ in FR SIP arrhythmicity ↑ in FR	Mean stride duration
(Nantel and Bronte-Stewart, 2014)	<i>N</i> = 15 FR <i>N</i> = 15 NFR	OFF/ON	SIP task	<i>OFF</i> : SIP asymmetry ↑ in FR ^a SIP arrhythmicity ↑ in FR Mean stride duration ↓ in FR <i>ON</i> : SIP asymmetry ↑ in FR SIP arrhythmicity ↑ in FR	Mean stride duration (ON)
(Killane et al., 2015)	<i>N</i> = 13 FR <i>N</i> = 7 NFR	ON	SIP, ST+DT Pre- and post-intervention	<i>Pre- and post-intervention, ST + DT</i> : SIP asymmetry ↑ in FR SIP arrhythmicity ↑ in FR Step cycle duration	No effect of SIP DT training
Turning					
(McNeely and Earhart, 2011)	<i>N</i> = 10 FR <i>N</i> = 10 NFR	OFF/ON	In-place 180° turns	Head rotation onset ↑ in FR	Trunk and pelvis rotation onset
(Bhatt et al., 2013)	<i>N</i> = 10 FR <i>N</i> = 10 NFR	ON	0°, 90°, 120° and 180° turns	Increased turning sharpness (180°): ↑ step width in NFR, not in FR	Step width, step width variability
(Spildooren et al., 2013)	<i>N</i> = 13 FR <i>N</i> = 14 NFR	OFF	180° turns, ST+DT, preferred and slow speed	Head rotation onset latency ↑ in FR Head-pelvis separation duration ↑ in FR	Head, trunk, pelvic rotation parameters (onset, separation, normalized velocity, average velocity), turning depth, no DT interaction
(Bengevoord et al., 2016)	<i>N</i> = 16 FR <i>N</i> = 14 NFR	OFF	180° turns	Step width ↓ in FR	CoM parameters (distance, velocity, medial- and anterior position)

Note: CoM, center of mass; DT, dual-task; FR, freezers; NFR, non-freezers; SIP, stepping in place; ST, single task

^a Not retained after correcting for confounders