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MOVEMENT DISORDERS (SA FACTOR, SECTION EDITOR)

Freezing of Gait in Parkinson's Disease: Where Are We Now?

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Abstract Freezing of gait (FOG) is defined as a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk. It is one of the most debilitating motor symptoms in patients with Parkinson's disease (PD) as it may lead to falls and a loss of independence. The pathophysiology of FOG seems to differ from the cardinal features of PD and is still largely unknown. In the present paper, we review the studies that were performed since 2011 on methods to provoke and assess FOG and discuss new insights into behavioral and neural mechanisms underlying this clinical phenomenon. We conclude that most of the work reviewed confirms that gait pattern generation disturbances are central to FOG. The finding that FOG reflects a combined motor and cognitive de-automatization deficit, which may not be sufficiently offset by executive control, probably acts as parallel mechanism.

Keywords Freezing of gait · Parkinson's disease · Neuroimaging · Cognition · Posture

Introduction

Freezing of gait (FOG) is defined as a "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [1••]. These short-lasting cessations of locomotion are most frequent in the later stages of PD (70 %) [2, 3] but also occur in 26 % of early-stage patients not yet exposed to levodopa therapy [4]. FOG is an incapacitating motor symptom, as it significantly affects patients' quality of life [5] and levels of activity [6]. FOG seems to develop independently of the cardinal features of PD and is not a consistent feature suggesting diverging pathological mechanisms [4, 7]. Although more prevalent with disease progression [8], FOG is more than merely a sign of advanced disease. Medical and rehabilitation treatment improve FOG but not to the same extent as other PD symptoms [9, 10].

A recent review, based on an NIH sponsored gathering of experts, described FOG as a "mysterious phenomenon" [1••] and proposed 5 directions for developing hypotheses on the pathophysiology of FOG, based on publications between January 1966 and April 2011. These 5 "hypotheses" attributed FOG to (1) abnormal gait pattern generation, (2) a problem with central drive and automaticity of movement, (3) abnormal coupling of posture with gait, (4) perceptual malfunction, and (5) frontal executive dysfunction. In the current paper, we will review the outcomes of the studies published since this seminal paper in 2011. We have selected all the material that bore a relationship with the different hypotheses put forward in the paper by Nutt et al. and discuss newly developed methods to assess FOG in a controlled setting.

New Methods of Assessment of FOG

One issue that substantially adds to the complexity of FOG research is that the freezing phenomenon is difficult to study in a research laboratory because of its unpredictability. Since the Nutt et al. review [1••], new approaches for provoking and measuring freezing episodes have been addressed, not only to evaluate the kinematic aspects of FOG, but also to adequately classify patients as freezers or nonfreezers. Although not a

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perfect paradigm, studying freezer/nonfreezer comparisons offers a window into possible mechanisms of FOG, that is, if the groups are equal for other disease characteristics. Most studies classified patients based on their subjective descriptions of FOG, either assessed by item 3 of the Freezing of Gait Questionnaire (FOG-Q) [11] or the New Freezing of Gait Questionnaire (NFOG-Q) [12]. Even though these FOG questionnaires proved reliable, it also became apparent that not all patients are able to give a correct appraisal of their own freezing problems [12].

To elicit FOG in a laboratory setting, and thus undoubtedly distinguish "definite" from "probable" freezers, objective examinations have been attempted; rapid 360° turns when "off" medication comprised the most effective test [13]. The combination of this task with walking while dual-tasking has a sensitivity of 96 %. Nantel et al. [14] recently validated a quantitative method to measure freezing episodes using a stepping in place task on force platforms. The specificity and sensitivity of this method to identify freezers reached 93 % and 87 %, respectively, but this method is less useful for a clinical setting. The current 'gold standard' clinical method to assess freezing severity is to identify the number of episodes during a standardized gait test, which can be videotaped and verified by other examiners [15]. Two clinical instruments for rating festination and FOG during FOG-eliciting circumstances have been validated and have shown a high inter-rater and test-retest reliability [16, 17]. Morris et al. [15] acquired video recordings during a timed up-and-go task from 10 definite freezers but found the number of freezing episodes to be only moderately reliable (intraclass correlation coefficient 0.63). Hence, a new metric was recommended: the percentage time frozen, ie, the cumulative duration of freezing episodes divided by the total duration of the walking task. However, the intraclass correlation coefficient remained moderate (0.73).

The review by Nutt and coworkers [1••] referred to an alternative objective measure of using a freezing index [18] based on spectral analysis of vertical leg movements. Delval et al. [19] extended this work by detecting FOG episodes triggered by treadmill walking while avoiding unexpectedly appearing obstacles. Time-frequency analysis of knee goniometer data identified very brief FOG episodes with a sensitivity of 75 %–83 % and specificity above 95 %. However, only 5 out of the 10 definite freezers experienced FOG episodes, pointing to the likelihood that the treadmill acted as a cue to overcome FOG [20]. Recent validity studies during over-ground performance of the timed-up-and-go task showed good correlations between clinical measures of FOG and various spectral analysis derived measures. These developments indicate that objective monitoring of FOG holds future promise to be used in standardized protocols [15, 21].

The above mentioned methods successfully investigate the behavioral aspects of FOG but are unsuitable for studying its underlying neural aspects using brain imaging. For this purpose, several alternative experimental approaches were validated as proxy-measures of FOG. Naismith and Lewis [22] developed a novel virtual gait paradigm in which participants navigated a realistic 3-dimensional virtual environment by depressing foot pedals. Though the use of pedals may reduce the chance of freezing [23], the outcomes on the virtual gait task correlated with patients' FOGQ scores. Subsequently, this paradigm was used in combination with functional magnetic resonance imaging (fMRI) [24]. Snijders et al. [25] used motor imagery (MI) of walking in freezing-provoking circumstances as a substitute for FOG in combination with fMRI. This method exploits the large functional and neural overlap between motor planning and MI [26, 27], and has been successfully used to study locomotion in healthy persons via fMRI [28–30]. Another experimental approach was based on recent evidence that the freezing phenomenon involves speech or movements of the upper limbs as well [31, 32]. Freezing during repetitive upper limb movements was found in 82 % of freezers classified by the NFOG-Q and was well-correlated with FOG but not disease severity [32]. This task can be performed inside a scanner environment, and opens a new avenue for neuroimaging research on freezing as a generic problem [32, 33].

New Evidence on the Behavioral Aspects of FOG

Table 1 outlines the contribution of recent studies to each of the hypotheses put forward by Nutt et al. [1••]. These studies are based on between-group comparisons of freezers and nonfreezers or controls and provide indirect evidence for the origins of FOG. We discuss the results of these studies in relation to the 5 hypotheses of Nutt et al. in the next sections.

Abnormal Gait Pattern Generation

Although FOG is a transitory phenomenon, freezers' abnormalities of gait also manifest outside actual freezing episodes [34]. A particularly influential idea is that FOG is caused by a gradual reduction in baseline stride length. Since Chee et al. [35] demonstrated that decreased step length is a precursor of the "sequence effect"; a regression of amplitude leading to FOG, novel work has contradicted the idea that scaling of amplitude is central to FOG. Thevathasan et al. [36] found that bilaterally stimulating the pedunculopontine nucleus (PPN) in 7 freezers improved FOG selectively, while background deficits in step length were not significantly altered. Alternatively, freezers did have a smaller baseline step length than nonfreezers, as was shown during treadmill walking in "off"-state [37]. Both medication and deep-brain stimulation of the subthalamic nucleus (STN-DBS) were shown to enhance

Table 1 Studies investigating the different hypotheses on the origins of FOG as put forward by Nutt et al. 2011

Hypotheses on the origins of FOG	Evidence	Study	Methodology	Main results
1. Abnormal gait pattern generation	+	Bhatt et al, 2013	Gait analysis	Freezers have an abnormal gait pattern during turning.
	+	Nanhoe-Mahabier et al, 2013	Gait analysis	Split-belt walking induces stride time asymmetry and variability in freezers.
	+	Peterson et al, in press	Gait analysis	Stepping coordination is worse in freezers.
	+	Snijders et al, 2011	fMRI + VBM	Freezers show altered brain activity in areas involved in regulation of step amplitude.
	+/-	Cowie et al, 2012	Gait analysis	Freezing is related to high stride time variability but not to reduced stride length.
	+/-	Williams et al, in press	Gait analysis	Manipulation of step amplitude and rhythm affects coordination in PD.
	-	Danoudis et al, 2012	Gait analysis	Gait coordination and asymmetry deficits do not predict FOG.
2. Problem with central drive/automaticity of movement	+	Arias, Cudeiro, 2010	Gait analysis	Auditory cueing reduces FOG in freezers.
	+	Lee et al, 2012	Gait analysis	Visual and auditory cues improve gait in freezers.
	+	Nanhoe-Mahabier et al, 2012	Gait analysis	Auditory cueing improves gait in PD patients with and without FOG.
	+	Snijders et al, 2012	Gait analysis	Dual tasking during gait augments the risk to induce FOG.
	+	Spildooren et al, 2010	Gait analysis	Dual tasking during turning augments the risk to induce FOG.
	+	Spildooren et al, 2012a	Gait analysis	Freezers benefit more from cueing than nonfreezers during turning.
3. Abnormal coupling posture & gait	+	Spildooren et al, in press	Gait analysis	Freezers have an abnormal head-pelvis coupling during turning.
4. Perceptual malfunction	+	Cowie et al, 2012	Gait analysis	The number of freeze-like events increases when walking through narrow doorways.
	+	Kostic et al, 2012	VBM	Freezers show GM atrophy in regions involved in visuomotor functioning.
	+	Lord et al, 2012	Visuospatial tests	Freezers have a dysfunction of dorsal occipito-parietal pathways.
	+	Nantel et al, 2012	Visuospatial tests	Freezers have a dysfunction in visuospatial perception and reasoning.
	+	Tessitore et al, 2012a	VBM	Freezers show GM atrophy in regions involved in visuomotor functioning.
	+	Tessitore et al, 2012b	rsfMRI	Freezers show reduced functional connectivity in visual networks in freezers.
	-	Cohen et al, 2012	Visuospatial tests	Freezers and nonfreezers do not differ in estimating door width while sitting.
5. Frontal executive dysfunction	+	Imamura et al, 2012	rCBF	Freezers show decreased brain perfusion in areas involved in cognitive functioning.
	+	Kostic et al, 2012	VBM	Freezers show GM atrophy in regions involved in executive functioning.
	+	Shine et al, 2013	fMRI	Freezers showed reduced activation in cognitive control network during virtual walking.
	+	Tessitore et al, 2012a	VBM	Freezers show GM atrophy in regions involved in executive functioning.
	+	Tessitore et al, 2012b	rsfMRI	Freezers have reduced functional connectivity in executive attention networks.
	+	Vandenbossche et al, 2011	Cognitive tests	Freezers showed impairment in conflict resolution.
	+	Vandenbossche et al, 2012b	Cognitive tests	Freezers have a deficit in response selection.

Studies marked with "+" offer confirmatory evidence, the ones marked with "+/-" are partially consistent with and the ones marked with "-" contradict the investigated hypothesis

stride length whereas stride time variability and freezing provoked by passing through an experimental doorway, only responded to medication [38]. Earlier work [39, 40] indicated that impaired control of rhythmicity, bilateral coordination, and gait asymmetry were the critical aspects of freezing. Similarly, 2 recent studies on turning and FOG reported that, contrary to nonfreezers, freezers showed increased step time variability and augmented cadence during turning, which was correlated with a higher number of freezing episodes [41, 42]. Also, coordination of stepping was differentially affected by turning and backward walking in freezers compared with nonfreezers [43].

While these findings confirm the relationship between FOG and abnormalities of gait pattern generation, it remains unclear whether amplitude rather than timing or coordination deficits are the most important in determining the etiology of FOG. Using a split-belt treadmill paradigm, Nanhoe-Mahabier et al. [44] recently showed that freezers adapted differently to imposed gait asymmetry than nonfreezers by increasing their stride time asymmetry and variability, pointing to a temporal mechanism. However, no freezing episodes were elicited in this study and using a treadmill may have influenced other gait outcomes artificially. A study of repetitive upper limb movement from our own lab showed that the manipulation of amplitude affected movement quality more profoundly than imposing frequency or coordination constraints [45]. Manipulation of step amplitude and rhythm separately and jointly towards values which could induce FOG was also investigated during walking [46]. As in upper limb movement, it appeared that imposing a synergism of a reduced scale and high frequency of steps induced a freezing-related coordination deficit [43], albeit without actually eliciting FOG. Danoudis et al. [47] demonstrated that gait coordination and asymmetry deficits in freezers were affected by step length control but did not consistently predict FOG.

Acknowledging that all gait measures are inter-dependent to an extent, the above findings fit well with a recent conceptual model of FOG [48•]. The model proposes that several gait malfunctions interact and incur a simultaneous deterioration of stepping, which then crosses a critical threshold of dysfunctional gait, triggering a FOG episode. The evidence reviewed here suggests that deficits of scaling and timing, over and above that of gait asymmetry and coordination as separate variables, are primary for reaching the triggering threshold.

A Problem with Central Drive and Automaticity of Movement

Recent work has shown that adding a cognitive dual task to gait or turning augments the risk for FOG [13, 41]. Although general cognitive resources were diminished in freezers compared with nonfreezers, no correlation was found between dual task gait performance and cognitive outcomes, excluding a mere cognitive explanation of the findings [41]. Therefore, the findings confirm that freezers have impaired central or internal drive of movement, as was put forward by Nutt et al. [1••]. In a recent review, Vandenbossche et al. [49•] suggested that FOG is a de-automatization disorder and extended this hypothesis from the motor to the cognitive domain. As such, FOG was suggested to reflect an impairment of cognitive automaticity largely regulated by the basal ganglia which may be insufficiently compensated for by controlled (executive) cognitive processes run by frontal networks. The best way to experimentally test "the automaticity hypothesis" is by imposing cueing as an external drive for movement. We compared the effects of cueing in freezers and nonfreezers during turning while "off" medication and demonstrated larger benefits on the temporal characteristics of gait in freezers than nonfreezers. Indeed, freezing episodes were concurrently reduced [50]. Positive effects of cueing on "off"-associated FOG were also reported by Arias and Cudeiro [51] and Lee et al. [52]. Importantly, these cueing-induced benefits in freezers persisted even in complex obstacle-loaded trajectories that are common in daily life and trigger FOG [53], showing that they prime the motor system even unconsciously.

An Abnormal Coupling of Posture with Gait

The inherent fall risk associated with FOG [54] makes it likely that an axial motor impairment also contributes to FOG, supporting the hypothesis that FOG is due to an abnormal coupling of posture and gait. Faulty coupling between postural preparation and the stepping command is most evident at gait initiation. Jacobs et al. [55] were able to experimentally provoke freezing-like behavior as part of multiple anticipatory reactions during a platform perturbation maneuver that elicits automatic protective stepping. Novel evidence for the axial contribution to the etiology of FOG came from studies showing that freezers had an abnormal head-pelvis movement coupling during turning in the "off state." This abnormality was already clear at turning onset and became more marked during trials including FOG episodes [56]. Interestingly, the FOG-episodes themselves tended to occur at the end of a turn or at the pivot point and not at turning onset. Whether this en-bloc pattern is a true axial marker of FOG, contributing to the 'threshold' for eliciting FOG during turning or merely a compensatory problem for increased postural control problems, is unclear. Postural instability is a general problem in PD, irrespective of FOG. In a multivariate model, fall and balance problems predicted FOG but to a lesser extent than cognitive and motor deficits [57]. Recent subgroup analysis in patients with Postural Instability/gait disturbance (PIGD) showed that freezers had a different genetic and clinical profile than nonfreezers [58]. These findings strengthen the possibility that freezers have a specific postural deficit, which does not necessarily generalize to patients who have postural instability

without freezing. Nantel and coworkers [14] showed that during repetitive stepping, freezers had underscaled and inefficient weight transfer between both legs associated with freezing episodes. Restricted axial movement in freezers could impact on lateral center-of-mass movement, which in turn would induce a delay or lack of stepping. Freezers also showed worse directional control of voluntary movement of the center of mass than nonfreezers, while moving a cursor on a computer screen (Vervoort et al., under review). This postural control deficit was more pronounced in backward-forward direction than in mediolateral direction and may explain the tendency to fall when patients cannot counteract the forward propulsion of hastening of gait in the run-up to FOG. Hence, more work is needed to refine the third hypothesis of FOG to unravel these mechanisms.

A Perceptual Malfunction

The fact that spatial constraints such as narrow doorways trigger FOG has led to the proposition that FOG results from a perceptual malfunction [1••, 59]. Narrowing door widths slowed down gait to a larger extent in freezers than nonfreezers and increased freezing-like events and FOG-frequency [38]. Freezers displayed increased within-trial variability of step length and step time which was exaggerated as doorway size decreased [59]. On the other hand, when estimating the door width while sitting, visual-spatial perception did not differ between freezers and nonfreezers [60]. Alternatively, encountering doorways may distract attention and as such elicit FOG or simply viewing a doorway may prime the motor system inappropriately towards adapting locomotion, as unconscious motor activation, or inhibition processes are dependent on dopaminergic input.

Neuropsychological assessment was also used to detect possible freezing-related deficits in visuospatial perception and reasoning. Freezers displayed a greater impairment in this area than nonfreezers, while executive function tests were equal in both subgroups [61]. Furthermore, Lord et al. [62] compared freezers and nonfreezers who were well-matched for basic visual and cognitive function on a distinct visuospatial task considered important for gait control, and a visuoperceptual task of object-form recognition. As expected, freezers showed a specific deficit of the visuospatial function. As a consequence, it was suggested that FOG evoked by doorway navigation or visual triggers may stem from a dysfunction of occipito-parietal dorsal stream processing.

Frontal Executive Dysfunction

Increasing evidence is emerging that patients with FOG show greater dysfunctions in executive control compared with nonfreezers [63•] and that these may contribute to FOG, independent of other factors [57]. Set-shifting difficulties under temporal pressure were found to specifically relate to freezing severity [64]. Vandenbossche et al. [65] found that the ability to suppress unwanted responses is impaired in both medicated and nonmedicated freezers, suggesting a nondopaminergic deficit. Freezers and nonfreezers did not show differences in other executive domains in this study. When examining the exact nature of response selection during confrontation with conflicting stimuli, freezers showed more erroneous and reflex-like behavior, suggesting a specific and automatic deficit in inhibition of unwanted responses [66]. This impairment of conflict resolution itself may offer an additional explanation for the paroxysmal nature of a FOG episode in conjunction with insufficient cognitive resources to compensate for this deficit. Hence, according to a recent cognitive viewpoint on FOG [49•], it may be that FOG is induced by a disturbed interplay between automaticity and controlled processing and that executive dysfunction thus plays a secondary role by limiting the ability to compensate for the loss of automaticity inherent to FOG.

New Evidence on the Neural Background of FOG

In 2008, Bartels and Leenders [67] reviewed the few brain imaging studies which had addressed the cerebral basis of FOG. They concluded that FOG may result from dysfunctional basal ganglia-thalamo-cortical circuitries, particularly those involving premotor and parietal areas. Since then, further work has investigated differences in brain structure and function between patients with and without FOG using voxel based morphometry (VBM), resting state functional magnetic resonance imaging (rsfMRI), fMRI, and single-photon emission computed tomography (SPECT).

Using VBM, it was found that grey matter atrophy in frontal and parietal cortices in freezers was associated with FOG severity, which was in turn correlated with frontal executive dysfunction [68]. The prefrontal areas, which showed reduced grey matter in freezers, were interpreted as central in performance monitoring and the allocation and coordination of attentional resources [69]. Tessitore et al. [70] correlated grey matter atrophy in the left cuneus, precuneus, lingual gyrus, and posterior cingulate cortex to clinical severity of FOG. Together, these findings offer support for the hypothesis that FOG is related to frontal executive dysfunction with at least shared underlying structural damage to the frontal and parietal cortices. However, the dorsolateral pathways also mediate visual input during locomotion such that structural abnormalities may contribute to perceptual malfunction in freezers as well. Importantly, differences in cerebral blood flow and resting state connectivity were reported in similar regions. Temporal correlations in brain activation between functionally related regions govern performance of many cognitively controlled tasks, even though subjects are at rest [71]. Such resting-state

functional connectivity was decreased in executive attention and visual networks in patients with FOG [72], correlating with FOG severity. Decreased brain perfusion, a measure of baseline metabolism, in prefrontal, orbitofrontal, and anterior cingulate regions in patients with FOG was found in comparison with nonfreezers by means of SPECT [73].

Task-related MRI studies investigating FOG are still sparse, since gait itself can not directly be studied in an MRI environment. Motor imagery of gait and stepping movements in a virtual-reality context have recently been used as alternatives to investigate neural correlates of gait planning in freezers. Patients with FOG exhibited decreased neural activation in the anterior insula, ventral (associative) striatum, supplementary motor area (SMA), and left STN, when facing complex cognitive cues during virtual walking [24]. Even though general cognitive abilities were similar between the 14 freezers and 15 nonfreezers, patients with FOG appeared less able to recruit a cognitive control network. Decreased BOLD responses in mesial frontal regions including the SMA and posterior parietal regions were found in 12 freezers during MI of gait [25]. Decreased SMA activity in freezers was associated with altered regulation of step amplitude, which would be in agreement with the hypothesized spatiotemporal deficit underlying FOG. In contrast, the mesencephalic locomotor region showed gait-related hyperactivity in freezers and reduced grey matter volume in a small portion of this region. Thus, both structural and functional alterations in this region distinguished freezers from nonfreezers. To summarize, recent neuroimaging studies, though limited by indirectly assessing gait control, support a dual mechanism underlying FOG. In this view, dysfunctional striatofrontal and downstream corticopontine pathways both play a critical role in the pathophysiology of FOG and may respond differently to contemporary medical treatment options.

New Evidence on the Responsiveness of FOG to Medical Treatment

Dopaminergic medication and STN-DBS primarily target the dopamine-deprived striatofrontal system inducing well-established benefits for cardinal symptoms of PD and spatiotemporal gait kinematics [74–78]. However, their effect on FOG proved more complex [9, 80]. With regards to levodopa responsiveness, 3 main types of FOG were identified [79•]. The most common type, "off" FOG, is relieved by administration of levodopa. In "levodopa-unresponsive" FOG, the levodopa dose adequately treats other symptoms, but not FOG, suggesting a different threshold for FOG and appendicular symptoms. Finally, in pure "on" FOG, FOG is absent during "off" periods but emerges after the first medication dose. Inconclusive effects of amantadine and selegeline have been reported recently in relation to FOG [73, 80, 81].

STN-DBS has shown mixed effects on FOG, depending on follow-up time and stimulation parameters [82–85]. Niu et al. [86] showed that FOG severity improved in STN-DBS-treated patients after 1 year. Combining levodopa and STN-DBS with methylphenidate, which enhances synaptic dopamine, was shown useful for treating "on" and "off" FOG [87]. However, a study on methylphenidate in PD patients with mild gait impairments (without STN-DBS) did not have an effect [88]. The fact that levodopa and STN-DBS enhance spatiotemporal aspects of gait control [75, 77], turning kinematics [76], coordination [78] and dual tasking [77] may explain their shared clinical benefits on FOG. However, the finding that freezing events triggered by a narrow doorway occurred less frequently after medication intake but did not differ in response to STN-DBS suggests that levodopa and STN-DBS may also exert treatment-specific effects on FOG [38].

Nondopaminergic disturbances are also under investigation with regards to FOG. Extrastriatal cell damage in the locus coeruleus, the PPN, and nucleus basalis of Meynert is well described in PD and down-regulates neurotransmitter systems other than dopamine, ie, noradrenaline, serotonin, glutamate, and acetylcholine systems [89, 90]. Noradrenergic deficits due to locus coeruleus cell loss have been associated with poor balance, falls, and possibly FOG [91]. There is data suggesting that the noradrenergic precursor L-threo-DOPS is effective in treating FOG [92]. The PPN is increasingly recognized as a heterogeneous neurochemical structure with mostly GABAergic neurons in the rostral part and cholinergic- and glutamatergic-expressing neurons in the caudal part [93]. Through dense connections with other regions [94, 95], the PPN governs several aspects of motor and cognitive functioning, among which are gait initiation and maintenance [94, 96, 97]. Evidence with regard to PPN-DBS on FOG is sparse (see [98] for a review). Mixed results were found in 6 patients with refractory postural instability and gait difficulty who had undergone previous STN-DBS [99]. However, DBS of a caudal PPN region recently proved effective in 5 patients with severe FOG and postural instability without concurrent improvements in spatiotemporal gait characteristics [36]. Besides postural and locomotor control, PPN stimulation may influence cognitive features of FOG. As recently reviewed by Yarnall et al. [100], cholinergic circuitries through the PPN and nucleus basalis of Meynert may be at the basis of cognitive dysfunction, gait disorders, and falls as well as their interplay, which may also be important for FOG.

Conclusions

We examined whether the field has moved forward with respect to 5 recently presented perspectives on FOG. When summarizing recent findings, abnormal gait pattern generation

seems to be a primary factor inherent to FOG, in which amplitude and timing dyscontrol act in synergy. The fact that this defective spatiotemporal control of movement also occurs in relation to freezing in other effectors strengthens the argument that this is crucial.

Problems with central drive and automaticity have been shown to be at the heart of freezing, and this review confirms that de-automatization in motor as well as cognitive functions may be more apparent in freezers than in nonfreezers. However, it remains unclear whether cognitive processes are hampered by this loss of automaticity or whether both automatic and cognitive deficits act in parallel and reinforce each other. Converging behavioral and neural evidence confirms that executive dysfunction plays a key role in FOG, as greater disruptions of the frontostriatal- parietal networks were correlated with freezing severity. Response selection under conflict resolution seems the primary freezing-related executive deficit.

Impairment in the visuospatial domain in freezers may be a key element of the perceptual malfunction hypothesis, which coincides with grey matter loss in posterior cortical regions and reduced functional connectivity in the visual network. Refinement of this hypothesis is indicated by studies addressing how visuospatial functions in relation to gait navigation may play a role in FOG. The exact nature of the postural deficit in coupling posture with gait has not been identified by recent study, but the control and scale of center of mass movements during gait may offer researchers a direction for further study. In sum, this review has shown that the field has moved forward since publication of the previous summary paper. It has illustrated that, with further refinements, the directions for studying the multifactorial nature of FOG still hold.

Conflict of Interest E. Heremans declares that she has no conflict of interest.

A. Nieuwboer declares that she has no conflict of interest.

S. Vercruysse declares that she has no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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