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Freezing of gait: moving forward on a mysterious clinical phenomenon

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Abstract

Freezing of gait (FoG) is a unique and disabling clinical phenomenon characterised by brief episodes of inability to step or by extremely short steps that typically occur on initiating gait or on turning while walking. Patients with FoG, which is a feature of parkinsonian syndromes, show variability in gait metrics between FoG episodes and a substantial reduction in step length with frequent trembling of the legs during FoG episodes. Physiological, functional imaging, and clinical–pathological studies point to disturbances in frontal cortical regions, the basal ganglia, and the midbrain locomotor region as the probable origins of FoG. Medications, deep brain stimulation, and rehabilitation techniques can alleviate symptoms of FoG in some patients, but these treatments lack efficacy in patients with advanced FoG. A better understanding of the phenomenon is needed to aid the development of effective therapeutic strategies.

Introduction

Freezing of gait (FoG) is an often dramatic, episodic gait pattern that is common in advanced Parkinson's disease (PD), other parkinsonian syndromes, and microvascular ischaemic lesions.[1–3] FoG highly impairs mobility, causes falls,[4,5] and reduces quality of life.[6,7] The pathogenesis of FoG is not understood and empirical treatments are of poor efficacy. For these reasons, FoG is an important clinical problem. It is also a challenge to our understanding of the physiology of normal locomotion in humans and the pathogenesis of gait disorders in patients.

In this Review, we describe the clinical features of and therapeutic approaches to FoG, discuss the physiology of locomotion in animals and humans, and consider hypotheses for the pathogenesis of FoG. This material is drawn, in part, from presentations and discussions at an international workshop (Freezing of gait: from clinical phenomena to basic mechanisms of gait and balance) on FoG held in February, 2010.

Clinical features

Although classic FoG is easily recognised, to define the phenomenon precisely is surprisingly difficult. The definition accepted at the 2010 workshop of clinicians and scientists interested in FoG was "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk."[8,9] This definition includes episodes in which the patient cannot initiate gait ("start hesitation") and arrests in forward progression

during walking ("turn" and "destination" hesitation), as well as episodes of shuffling forward with steps that are millimetres to a couple of centimetres in length. The notion of FoG as an episodic phenomenon is important because it suggests transient disruptions of locomotor circuitry. Most commonly, FoG lasts a couple of seconds, but episodes can occasionally exceed 30 s.[10] Rarely, FoG seems to be almost continuous, such that the patient is unable to generate any steps that are long enough to provide useful ambulation.

Several important features can accompany FoG: (1) the foot or toe does not leave the ground or only barely clears the support surface; (2) alternate trembling of the legs occurs at a frequency of 3–8 Hz;[11–13] (3) hastening, or an increase in cadence with a decrease in step length, often precedes FoG;[14] (4) a subjective feeling of the feet being glued to the floor accompanies episodes of freezing; (5) FoG is commonly precipitated or relieved by various cues; and (6) FoG can be asymmetrical, affecting mainly one foot or being elicited more easily by turning in one direction.

If one or more of these associated features is universal to all episodes of FoG, they could provide important clues to its pathogenesis. Alternatively, some of these features could help with identification of different forms of the disease; that is, FoG might not be a single clinical phenomenon but represent several different syndromes with different underlying mechanisms. Along this line of reasoning and on the basis of clinical findings, three different patterns have been suggested: (1) trembling in place: alternating tremor of the legs (knees); (2) shuffling forward: very short, shuffling steps; and (3) complete akinesia: no movement of the limbs or trunk, but this pattern is uncommon.[10] The bottom line is that the clinical and physiological heterogeneity of FoG prohibits a universally accepted definition.

The likelihood that FoG will occur depends on the situation. It most commonly occurs when a person is starting to walk, turning, passing through narrow passages, or approaching a destination such as a chair. Although less likely, FoG can also occur while walking straight ahead in open spaces. Environmental influences, along with emotional and cognitive situations, can have striking effects on FoG. Circumstances that precipitate FoG include approaching doorways, dual-tasking, distractions, crowded places, and being under time pressure. Circumstances that ameliorate FoG include emotion, excitement, auditory cueing at the proper pace, targets for stepping, and climbing stairs.[15] One notion that might tie the precipitating and ameliorating features together is their effect on the patient's attention. Conditions that distract the patient from walking will promote FoG and those that focus attention on stepping will reduce it, consistent with a cortical take-over of impaired subcortical control of gait.[16] An unanswered question is whether the conditions that precipitate and ameliorate FoG are important clues to its pathogenesis or whether they indicate compensatory mechanisms used by the brain to overcome a more fundamental dysfunction causing FoG.

Festination while walking is defined clinically as a tendency to move forward with increasingly rapid, but ever smaller steps, associated with the centre of gravity falling forward over the stepping feet.[8] James Parkinson was fascinated by festination. He described how the patient with PD was "thrown on the toes and forepart of the feet; being, at the same time irresistibly impelled to take much quicker and shorter steps ..."[17] The relation between

festination and FoG is an important issue. If festination precedes most interruptions of ongoing gait, FoG could be viewed as a more general phenomenon of interruption of other motor tasks, such as repetitive hand movements or speech, in which similar events are also seen. However, it is difficult to incorporate festination into the problem of gait initiation (start hesitation) encountered by most patients with FoG. Alternatively, festination might be another episodic, but separate, gait disturbance frequently present in patients with FoG.

Patients with PD are typically divided into those with and without FoG. However, neither history-taking from the patient and caregiver[18] nor physical examination[15,19] can reliably determine whether a patient has FoG. In fact, the question is not only whether this simple grouping is feasible in practice and in scientific studies, but whether this division portrays the true nature of FoG. Perhaps it is better to score patients along a continuous spectrum of freezing severity, ranging from no freezing at all at one end, to severe FoG at the other end.[15] To complicate matters, results from studies[20,21] showed that healthy people could have brief episodes of alternate leg trembling with delayed step initiation resembling FoG if they had to wait for instructions about which leg to step with.

FoG in PD is associated with disease severity and longer levodopa treatment[2,3], although it can be seen early in the course of the disease and in untreated patients.[22] Despite its relation to disease severity, FoG does not correlate with the cardinal features of parkinsonism: tremor, bradykinesia, or rigidity.[22,23] This should not be surprising since FoG occurs in syndromes without parkinsonism,[24] or can be the first presenting feature in parkinsonism. FoG does correlate with other midline signs, speech disturbance, and postural instability,[22] and with cognitive decline, particularly executive dysfunction.[25–27] Within executive dysfunction, set-shifting and conflict resolution are particularly impaired in PD patients with FoG.[26,28] Visual abnormalities, depression, and anxiety are also more frequent in patients with FoG.[22,27,29,30]

Physiological characteristics

Continuous gait abnormalities

Gait abnormalities are present between freezing episodes in patients with FoG. Locomotion in such patients is characterised by increased variability of step timing,[31] disordered bilateral coordination,[31,32] and a reduction of stride amplitude.[33] Patients with FoG also increase their cadence to abnormally high rates during a turn compared with patients without FoG and healthy individuals.[34,35] These continuous gait and turning deficits are unrelated to disease severity or asymmetry,[33,35,36] but are related to postural instability,[37] suggesting that FoG and postural instability are in some way connected.[4,5,8] The high risk of falling in patients with FoG might therefore result not only from FoG itself, but from the associated balance impairments. These gait and turning abnormalities are more pronounced in patients with PD when the dopaminergic drug effects are at their nadir (the patient is in the off state), implicating a dopaminergic contribution to FoG in PD.[37] This non-episodic or continuous gait deficit (which affects the timing, scaling, and coordination of stepping) might culminate in FoG. This notion is supported by studies in which the spatiotemporal demands on gait were experimentally manipulated. Patients with FoG have more difficulty in adjusting their step length to a fast metronome beat than do those without FoG and, at higher frequencies,

FoG might be induced in patients predisposed to FoG.[38,39] Similarly, imposing very short stride lengths elicits a ‘sequence effecf: a step-by-step regression of amplitude that can lead to FoG in patients with PD who are predisposed to the phenomenon.[33] The induction of an asymmetrical stepping pattern, such as that required during 180° turns, also leads to FoG, possibly as a result of a shorter step length required by the inner foot of the turning arc.[10,13,15,35] Finally, in patients with PD who were treated with deep brain stimulation, a 50% reduction of subthalamic nucleus stimulation contralateral to the leg with the longer step length reduced FoG, presumably by induction of a more symmetrical gait.[40] However, it should be noted that the interlimb incoordination in patients is not limited to the legs—it is also present in the arms.[41]

Episodic abnormalities

When a patient is walking forward, the physiological events immediately preceding and during an episode of FoG are characterised by one or more of the following features: (1) a profound and incremental decrease in stride length;[33,42] (2) highly reduced joint ranges in the hip, knee, and ankle;[42] (3) disordered temporal control of gait cycles, which is difficult to distinguish from festinating steps;[14,43] and (4) high-frequency alternate trembling-like leg movements (figure 1). Spectral analysis of these high-frequency leg oscillations shows that various abnormal power peaks occur in the frequency bands of 3–8 Hz.[11,12,13,19] The complexity and unevenness of the energy spectrum affected cannot be explained by tremor. These leg oscillations are so common in episodes of FoG that they have been used to detect this phenomenon with ambulatory monitoring.[13,44] An important implication of these leg or knee oscillations is that FoG is usually not just akinesia—movement exists but it does not produce the desired goal of walking.[12]

Electromyographic analysis of episodes of FoG confirms the presence of abnormal activity,[11] but also suggests that these episodes cannot be explained by increased co-contraction of lower-limb muscles or by tremor.[11,43] Although highly variable patterns of muscle activation occur, the reciprocal activation of agonists and antagonists is preserved in most cases, but the onset and termination of muscle activation might be premature.[11] Furthermore, electromyographic profiles of leg muscles immediately before an episode of FoG show hastening and decreasing bursts of gastrocnemius activity.[43]

With the exceptions noted above, capturing FoG in the laboratory has generally been difficult, so few physiological recordings of start hesitation and freezing during walking exist. However, new methods to induce FoG in the laboratory[18,45] and ambulatory devices for capturing FoG[13] should soon expand its physiological characterisation.

Freezing in other motor tasks

Freezing is not restricted to locomotion. Motor blocks have been reported to occur in alternating repetitive movements of the fingers[46,47] and during speech.[48] The kinematic patterns of upper-limb freezing resemble those of FoG and their severity correlates with the severity of FoG (figure 2).[47] The high-frequency components and gradual reduction in amplitude of finger flexion during the episode of freezing are features that overlap with FoG (figure 2).[47] These findings suggest that some types of FoG might be related to a general

motor deficit affecting the timing-amplitude control in different movement effectors and are not restricted to the locomotor network.

Locomotion and balance circuits

Freezing during walking involves either or both of two concomitant motor control processes: balance and locomotion. Balance controls postural (axial) tone, giving stability to the upright stance and allowing rhythmic movement of the legs to propel the person through the environment. Balance and locomotion are not just motor systems; the afferent systems that provide sensory feedback to the balance and locomotor generators are also crucial to normal function. Thus, disruption in many areas of the CNS could be responsible for FoG.

The basic pattern of locomotion—that is, the rhythmical movement of the legs—is generated in the spinal cord. Central pattern generators for locomotion are networks of neurons that, in humans, seem to be dispersed over several spinal segments.[49] FoG could be caused by disrupted descending control of these spinal networks.

A hierarchy of supraspinal regions sends descending control signals to the spinal central pattern generators to modify the stereotyped locomotor pattern generated by these networks (figure 3). This supraspinal control is necessary for initiating gait, turning, stopping, avoiding obstacles, and otherwise adapting locomotion to the person's goals—the same situations that tend to induce FoG. The most important supraspinal regions involved in locomotion are the pontomeduUary reticular formation, the mesencephalic locomotor region (MLR), the basal ganglia, and frontal cortical regions.

The brainstem reticular formation is composed of many nuclei and is the origin of several descending pathways to the spinal cord.[50] The medullary reticular formation sends an important glutamatergic facilitatory pathway to the spinal central pattern generators.[51] Other excitatory pathways arise from the median raphe and parapyramidal region serotonergic neurons, locus coeruleus noradrenergic neurons, and lateral hypothalamus dopaminergic neurons.[51] The serotonergic neurons from the parapyramidal region are particularly important because they are among the first to stimulate locomotion during development and are also active during locomotion in adult animals.[51] Serotonergic antagonists reduce or abolish locomotor patterns in rodents, but the contribution of serotonergic pathways to FoG in humans is unknown.[51]

Descending inhibitory influences from the medullary reticular formation are also important for postural tone and stability. Activity in this inhibitory pathway is modulated by cholinergic input from the pedunculopontine nucleus (PPN). The stimulation of PPN cholinergic neurons induces atonia in decerebrate cats.[50,52]

The MLR is a region of the midbrain that, when stimulated, increases postural tone and induces stepping, or even running, in the decerebrate cat.[53] Coordination between anticipatory postural adjustments and stepping probably occurs in the MLR as well, because the activity of some MLR neurons is correlated with both postural and stepping movements.[54,55]

The major nuclei of the MLR are the PPN pars compacta (PPNc) and PPN pars dissipata (PPNd), the cuneiform nucleus, and the subcuneiform nucleus. The PPNc is mainly cholinergic, whereas the PPNd includes cholinergic, glutamatergic, GABAergic, and even noradrenergic and dopaminergic neurons. The PPN provides descending inputs to the pontomedullary reticular formation and to the spinal cord. It is also connected rostrally to the basal ganglia and the thalamus.[56,57] Which of these nuclei is actually the MLR is debated. Recordings from humans show that there is a modulation of activity in subcuneiform neurons with mimicked locomotion.[58] The cholinergic neurons of the PPN are particularly important for gait, as shown by several observations: (1) more degeneration of cholinergic neurons in patients with PD who have impaired balance; (2) balance deficits in l-methyl-4-phenyl-l,2,3,6-tetra-hydropyridine (MPTP)-treated monkeys with a loss of cholinergic neurons; and (3) posture and gait abnormalities induced in monkeys with cholinergic lesions in the PPN.[59]

Corticostriatal activity, facilitated by striatal dopamine, is important in determining which motor programmes are active at any point in time. Brainstem motor programmes are usually suppressed by tonic inhibition from the basal ganglia and excited by direct cortical input.[60] The activation of selected motor programmes follows the integration of cognitive, sensory, and limbic cortical inputs to the striatum and consequent disinhibition of the appropriate brainstem motor systems.[60–62] The basal ganglia output to the MLR is largely via the globus pallidus interna (GPi) in humans,[56,57] mediated by GABAergic neurons that tonically inhibit the MLR. Direct injections of GABAergic antagonists into the MLR can initiate locomotion.[60,62] Facilitation of the corticostriatal input by dopamine is critically important because dopaminergic replacement reduces FoG in patients with PD.[10]

The frontal cortex projects heavily to the brainstem reticular nuclei and the striatum, and is important for both postural control and locomotion.[63] Although a decerebrate cat can walk on a treadmill, its locomotion is stereotyped, showing no adaption to the environment or to the animal’s goals. Under normal circumstances, neurons in the primary motor area, the premotor cortex, and the supplementary motor area fire in relation to stepping and postural adjustments.[64,65] These cortical neurons, which project directly to the pontomedullary reticular formation and the spinal cord,[64] are envisioned as excitatory, balancing the inhibitory influences of the basal ganglia.[60] Clinicians recognise the particular importance of the frontal cortex and the basal ganglia in higher level gait disorders that often include FoG.[66] However, other cortical areas are also important in the control of gait, as shown by the effects of emotion and sensory inputs on walking in people with FoG.

Neuroimaging of walking

The importance of the balance and locomotor network identified physiologically has been supported by functional imaging studies in man during actual or imagined walking. The table summarises the brain areas activated during normal gait.

Functional imaging has also been used to compare patterns of activation between healthy people and patients with PD. Using SPECT to compare patients with PD to age-matched controls, researchers found less activity in the left medial frontal area, the right precuneus,

and the left cerebellar hemisphere, and increased activity in the left temporal cortex, the right insula, the left cingulate cortex, and the cerebellar vermis during walking.[67] Transverse lines on the walking surface, which are known to improve walking in patients with FoG, led to increased activation of the lateral premotor cortex, suggesting the importance of compensatory mechanisms to initiate and maintain walking in patients with PD.[72] Similarly, SPECT scanning during walking in patients with gait disturbances attributed to small vessel disease (vascular parkinsonism) showed relative underactivation of the supplementary motor area, the thalamus, and the basal ganglia, with relative overactivation of the premotor cortex.[73] A comparison of fMRI activation during imagined walking in patients with PD and matched controls showed less activation in the superior parietal lobule and the anterior cingulate cortex of patients.[74] When the patients were divided into those with and without FoG, patients with FoG showed more activation in the posterior mid-mesencephalon than those without, with a trend to decreased activity in the mesial frontal and posterior parietal cortices.[74] Structural changes in the midbrain—specifically, decreased grey matter in a part of the MLR—have also been suggested in patients with FoG.[74] Additionally, diffusion tensor imaging points to decreased connectivity between the PPN and the cerebellum in patients with PD and FoG.[75]

Clinical-pathological correlations

Although structural lesions or pathological processes rarely affect precisely a region of interest, relatively focal lesions suggest that the midbrain, the globus pallidus, the subthalamic region, and the supplementary motor area are involved in FoG. More diffuse disease processes implicate the frontal lobe and the basal ganglia (panel). These clinical findings provide further evidence for the importance of regions involved in the locomotor and postural networks highlighted in the physiological and neuroimaging sections of this Review.

Hypotheses for pathogenesis

We review five promising, not necessarily exclusive, hypotheses on the pathogenesis of FoG, organised from the most peripheral (central pattern generators in the spinal cord) to the most central (the frontal lobe).

Abnormal gait pattern generation

Impaired gait rhythmicity, and gait cycle coordination, even in the absence of clinically apparent FoG, could be due to abnormal output from the central pattern generators of the spinal cord.[8,13,37] The sequence effect of a progressive shortening of step length before freezing episodes[33] is another form of spatial-temporal incoordination, suggesting disrupted pattern generation. Disordered supraspinal facilitation might hinder the smooth running of central pattern generators, resulting in high-frequency oscillations in both the lower and upper limbs during freezing episodes.[11,12,47] These abnormalities could indicate a generalised problem with the coordination of rhythmic movement, because people with FoG are more likely to have gait incoordination between episodes of the phenomenon,[31,32,36] and during bilateral, upper-extremity, antiphase tapping.[47]

A problem with central drive and automaticity of movement

As skilled movements such as gait and posture become learned, they become automatic and require less attention. Implicit learning and automatic task performance is impaired in people with PD and might be more affected in patients with FoG.[89] Impairment in automaticity would explain why freezing occurs more often during the performance of another task such as talking or using a cell phone while walking.[35] Additionally, step initiation is usually internally generated and therefore more dependent on the basal ganglia than when externally generated by visual or auditory stimuli.[89] Loss of automaticity would also explain why patients with FoG benefit so much from external cues to drive their stepping pattern.[16] Thus, FoG could result from disruption of the basal ganglia–supplementary motor area loop for self-initiated movement, with walking becoming dependent on external cues that compensate via the cerebellum–dorsal premotor cortex to maintain a central drive for locomotion. Increased activity in the MLR of patients with FoG might also offer a compensatory drive to maintain gait in the face of dysfunction in the basal ganglia-supplementary motor area loop.[74] An alternative hypothesis of abnormal central drive proposes that FoG is triggered by episodically induced cross-talk of complementary, yet competing, basal ganglia inputs from motor, cognitive, and limbic cortical areas.[90] In this model, momentary synchronous firing in the output nuclei of the basal ganglia leads to increased inhibition in brainstem locomotor areas and consequently to FoG. To overcome an episode of FoG, the patient focuses on alternative, goal-directed behaviour to reset basal ganglia output.

Abnormal coupling of posture with gait

Stepping necessitates anticipatory postural adjustments to sequentially shift the body weight laterally and forward before the step. The hypothesis that FoG is caused by a problem in coupling these adjustments with stepping comes from the observation that the knee trembling that occurs in patients during FoG episodes resembles alternating, repeated anticipatory postural adjustments (figure 4).[45] These repetitive adjustments suggest that basal ganglia mechanisms for preparing a motor programme in advance of step initiation might be disrupted. Healthy controls make two, but not more, anticipatory postural adjustments before step initiation when the stepping leg is not defined until just before the step, suggesting that the trembling of the knees in FoG might be a compensation for impaired advance coupling of posture with gait.[21] The breakdown in coupling between posture preparation by the supplementary motor area and step initiation by the motor cortex might occur in the pontomedullary reticular formation, where posture and gait are coordinated.[54]

A perceptual malfunction

The well known problem of patients freezing when attempting to walk through a doorway suggests a problem with perceptual processing of the environment for navigation. In fact, perceptual processing of environmental constraints results in a slowing of gait in proportion to the width of the doorway in healthy participants.[91] Patients with PD and FoG decrease their gait speed and stride length to a much greater degree as a doorway is approached, suggesting an exaggerated response to action-relevant visual information for gait that could

explain FoG.[92,93] However, the ability to perceptually judge doorway width while sitting was not different between patients with FoG and healthy controls.[92] Thus, no evidence exists to support the hypothesis that a simple visual-perceptual processing deficit can explain the phenomenon. Deficits in complex online planning of locomotor adaptation based on changes in the environment need further investigation.

A consequence of frontal executive dysfunction

Executive dysfunction—that is, set-shifting, attention, problem solving, and response inhibition—are impaired in people with PD who have FoG compared with those without.[25,26,94] FoG frequently occurs when turns or obstacle avoidance require a switch in motor programmes. This ability to change motor programmes quickly is thought to involve basal ganglia processing of information from complementary, but competing, motor, cognitive, and limbic inputs.[90] Similarly, FoG is more likely during challenging walking tasks that require more attention, problem solving, and inhibition of inappropriate responses, as well as set-shifting, which is again consistent with a role for executive dysfunction in FoG.[74] However, as not all PD patients with executive dysfunction show FoG, further refinement of this hypothesis is needed.

Assessment and treatment

Episodes of FoG are often rare or absent in the clinic, so histories or questionnaires are often better indicators than clinical observations of the presence and severity of the phenomenon. However, FoG episodes can be mistaken for akinesia related to the off state, or the episodes can be so brief that they are ignored by the patient and family members. The revised unified Parkinson's disease rating scale includes items related to FoG severity,[95] but they have not been specifically validated for the assessment of FoG. Two validated questionnaires for this assessment are the original FOG-Q[96] and the New FOG-Q.[18] A newly developed severity score for FoG, based on observations of gait during circumstances that trigger the phenomenon, has a high inter-rater and re-test reliability, but might not reflect FoG during daily activities.[97] Methods for the objective recording of locomotion and the identification of these episodes with inertial sensors on the legs or trunk are currently being explored and might allow in future the assessment of FoG over long periods of time at home.[13,19,44]

FoG in PD occurs more frequently, but not exclusively, in the off state.[10] Therefore, manipulation of levodopa to keep the patient in the on state for more of the time is the most common treatment to reduce the occurrence of FoG. However, occasionally, FoG is made worse by levodopa,[98] and in this case lowering dopaminergic stimulation might alleviate the symptoms. Monoamine oxidase type-B inhibitors have been associated with a decreased likelihood of developing FoG in a large randomised, controlled study,[22] but they rarely reduce freezing once it has developed. Similarly, studies of dopaminergic agonists have shown that FoG is more common in the patients receiving agonists than in those receiving placebos,[99] but withdrawing dopaminergic agonists rarely improves FoG. Other drugs, such as amantadine, L-threo-dihydroxy-phenylserine, selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, methyl-phenidate, and botulinum toxin

injections in leg muscles have been reported to be helpful for patients with FoG in open-label studies or anecdotal reports.[100]

Rehabilitation approaches to FoG have received much attention in the last decade. Attentional strategies and cueing are used by patients successfully to overcome FoG[16,101,102] and can be modestly effective in the home.[103,104] A cane with a laser light visual cue also had a modest effect in people with FoG.[105] A device that can be used to detect episodes of the phenomenon and activate rhythmic auditory stimulation is under investigation.[44] Other rehabilitative strategies include group exercise[106] and treadmill training with auditory and visual cues.[107]

Deep brain stimulation of the subthalamic nucleus can alleviate symptoms of FoG, especially in the off state.[79,108] However, in a subgroup of patients with PD, FoG was induced by deep brain stimulation of the subthalamic nucleus.[79] Reducing the frequency of stimulation has also been reported to reduce FoG in some patients.[109] The use of deep brain stimulation of the PPN for FoG is under investigation; initial open-label results were positive although subsequent reports have been less promising.[110]

Conclusions

The big mysteries about FoG remain. The first mystery concerns the events that occur during episodes of FoG. Are there universal features in all episodes regardless of the varied clinical patterns[10] and diseases[1] producing FoG? Alternatively, are we pulling together several clinically similar but physiologically distinct phenomena? Most electromyographic or force-plate recordings of FoG episodes do not show absent movement as suggested by the term ‘freezing’. Rapid movements of the legs occur without forward progression, the so-called trembling knees. Understanding what these movements represent is important in understanding the pathogenesis of FoG. Finally, is FoG the same physiological phenomenon as freezing in hand movements[47] or during speech?[48] Alternatively, does the necessity of coupling locomotion with postural control make FoG different? These questions might be answered soon by new and more reliable methods to induce FoG, and with better technology to measure the clinical phenomenon.

A second mystery is how much of the phenomenology of FoG represents compensatory mechanisms as opposed to the actual causes of FoG. For example, the influences of various stimuli that can precipitate FoG or reduce the phenomenon might be acting via cortical mechanisms that are compensatory mechanisms needed for walking when automatic walking fails. The critical question might be, why does automatic walking fail rather than, why do doorways precipitate FoG?

Another mystery is the role of the frontal lobe and the basal ganglia in the engagement and modulation of the brainstem postural and locomotor circuits that underlie walking. Although it would be premature to draw any final conclusions, the fundamental disturbances in FoG do seem to come from frontal dysfunction produced by abnormal output from diseased basal ganglia, frontal disorders, or disconnection of the frontal lobes from subcortical and

brainstem nuclei, coupled with a dysfunctional MLR caused by intrinsic degeneration or abnormal input from striatal and cortical areas.

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Panel: Clinical–anatomical correlations—brain regions affected by various disease processes that have been associated with freezing of gait

Midbrain

- Pontomesencephalic junction haemorrhage[76]
- Midbrain infarcts[77,78]

Subthalamic region

- Deep brain stimulation of the subthalamic nucleus[79,80]

Globus pallidus

- Carbon monoxide[81,82]
- Pallidal degeneration[83]
- Pallidotomy[84]

Basal ganglia

- Parkinson's disease[2]
- MSA, PSP, CBD, DLB[1]

Supplementary motor area

- Infarct[85]
- Tumor[86]
- Focal atrophy[86]

Frontal lobe

- Normal pressure hydrocephalus[1]
- Vascular parkinsonism[1,87,88]

MSA=multiple system atrophy. PSP=pregressive supranuclear palsy. CBD=corticobasal degeneration. DLB=dementiawith Lewy bodies.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms “freezing of gait”, “gait ignition”, and “festinating gait”, between January, 1966 and April, 2011. We also identified articles through searches of the authors’ own files and the bibliographies of pertinent articles. Only articles published in English were reviewed. The choice of articles to include in this Review was based on the quality of each study, the pertinence to the topics reviewed here, the general availability of the reference source, and the opinions of the six authors and the participants of the workshop Freezing of gait: from clinical phenomena to basic mechanisms of gait and balance.

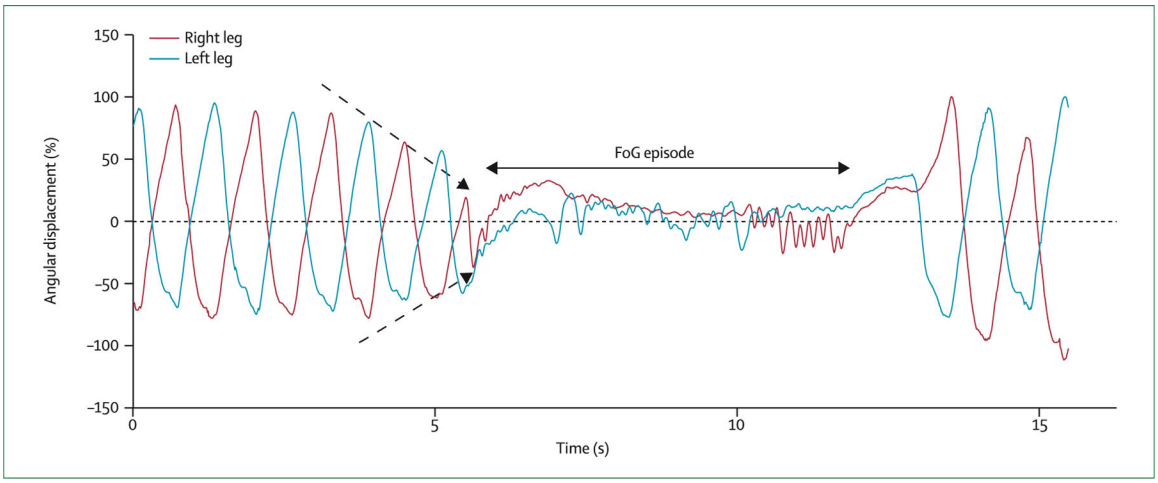

Figure 1: Illustration of FoG in a patient with Parkinson's disease

The tracing shows the angular displacement of the knees (% maximum knee angle) measured with an eight-camera Vicon optical motion capture system during a gait trial with FoG. The gait cycles before the freezing episode show a progressive decrement of step length as indicated by the dashed arrows. During the episode of FoG, irregular, rapid knee trembling is apparent. FoG=freezing of gait.

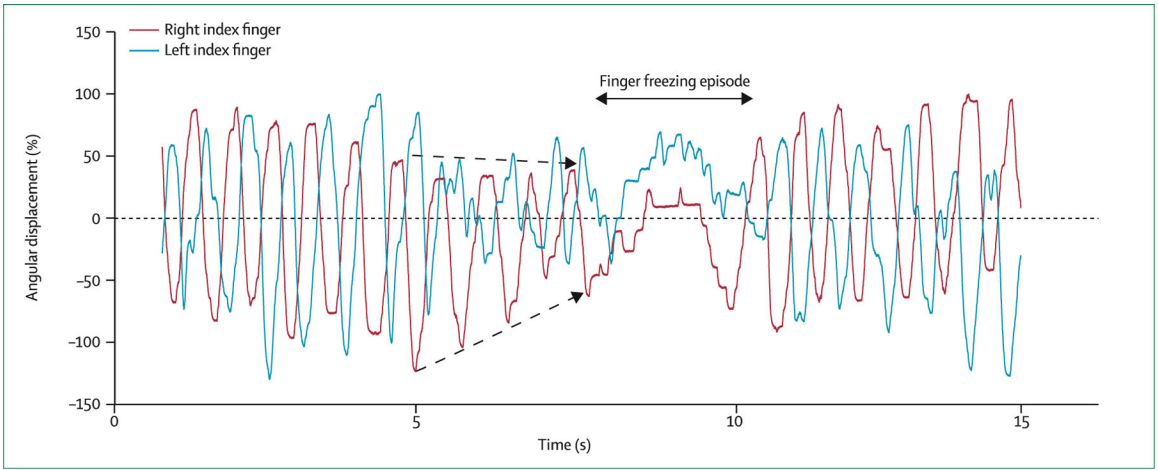

Figure 2: Example of freezing during repetitive finger movement

The angular displacement of alternating right and left finger flexion (% maximum flexion angle) measured with potentiometers placed on the fingers is shown during atrial with upper-limb freezing. The disturbance of the regular motion preceding the freezing episodes is characterised by amplitude regression as indicated by the dashed arrows. During the episode, irregular finger trembling is apparent.

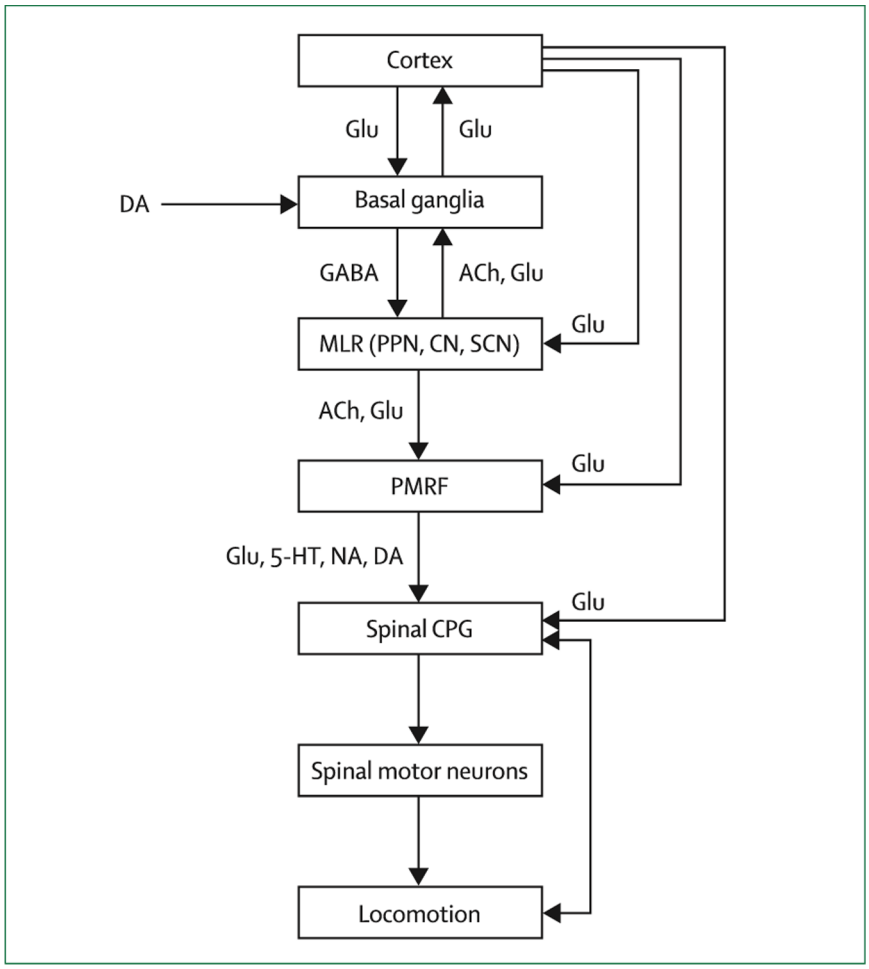

Figure 3: CNS circuitry controlling locomotion and balance

5-HT=serotonin. ACh=acetylcholine. CN=cuneiform nucleus. CPG=central pattern generator. DA=dopamine. Glu=glutamate. MLR= mesencephalic locomotor region. NA=noradrenaline. PPN=pedunculopontine nucleus. PMRF=pontomedullary reticular formation. SCN=subcuneiform nucleus.

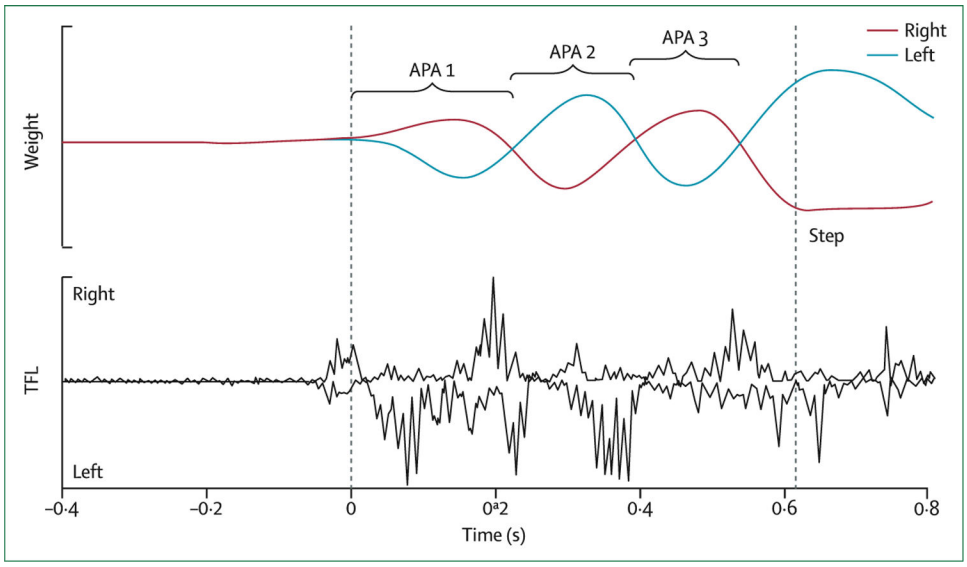

Figure 4: Knee trembling when attempting to initiate a step in a patient with Parkinson's disease and freezing of gait

The vertical forces, measured with force plates under each foot, shows repeated lateral weight shifting and reciprocal activation of left and right hip abductors, the tensor fasciae latae (TFL) muscles, measured with surface EMG. The pattern resembles repeated anticipatory postural adjustments (APAs) that normally occur only once to unload the stepping leg. The first vertical line is at the onset of the APA and the second line is at the onset of the step. Reproduced from Jacobs and colleagues,[45] by permission of Elsevier.

Table:

Brain areas activated during actual and imagined walking, compared with resting state, in healthy participants

	Number of participants	Paradigm	Technique
Brainstem			
MLR	10	Walked on a treadmill at 13 m/min to simulate the hypokinetic speed of patients with Parkinson's disease	SPEC[67]
MLR	16	Walked on the floor at a comfortable speed of 66 m/min	FDG-PET[68]
MLR	26	Imagined standing, walking, and running while lying supine in an MRI scanner	fMRI[69]
MLR	15	Imagined walking at normal and faster than normal gait speeds	fMRI[59]
Cerebellum			
Vermis	..	See above for details of study paradigms and numbers of participants	SPECT,[67] FDG-PET,[68] fMRI[59,69]
Basal ganglia			
Striatum and pallidum	..	See details above	SPECT,[67,70] fMRI[68,69]
Cortex			
Supplementary motor area	8	Walked on a treadmill at 17 m/min	NIRS[71]
Supplementary motor area		See details above	SPECT,[67] fMRI[59,68,69]
Lateral premotor cortex		See details above	SPECT[67]
Medial primary sensorimotor cortex		See details above	SPECT,[67] FDG-PET,[68] NIRS[71]
Cingulate cortex		See details above	SPECT,[66] fMRI[67,68]
Parahippocampal cortex		See details above	FDG-PET,[67] fMRI[67,68]
Superior parietal lobe (cuneus and precuneus)		See details above	SPECT,[66] FDG-PET,[67] fMRI[67,68]
Occipital cortex			fMRI[67,68]

FDG-PET=fluorodexoyglucose PET. fMRI=functional MRI. NI RS=near-infra red spectroscopy. MLR=mesencephalic locomotor region.