Review

The Next Step: A Common Neural Mechanism for Freezing of Gait

The Neuroscientist
2016, Vol. 22(1) 72–82

DOI: 10.1177/1073858414559101
nro.sagepub.com
SAGE

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Abstract

Freezing of gait is a disabling symptom of Parkinson's disease that causes a paroxysmal cessation of normal footsteps while walking. Despite a great deal of empirical research, the pathophysiological mechanisms underlying the symptom remain unclear. In this targeted review, we synthesize recent insights from research into freezing in an effort to clarify the neurobiological basis of this phenomenon. We conclude that freezing manifests via a common neural pathway in which transient increases in inhibitory basal ganglia output lead to decreased activity within the brainstem structures that coordinate gait. This cascade may be triggered through dopaminergic depletion in the striatum and over-activity within the subthalamic nucleus. These insights may benefit both the diagnostic and therapeutic management of freezing in Parkinson's disease.

Keywords

freezing, Parkinson's disease, conflict, subthalamic nucleus

Introduction

Freezing of gait (FOG) is a devastating symptom of Parkinson's disease (PD) that affects more than half of the people with advanced disease (Giladi and others 1992). Despite commonly occurring during gait, freezing has also been convincingly demonstrated in other behavioral domains, including foot-tapping, speech, and handwriting (Lewis and Barker 2009; Nutt and others 2011). FOG also occurs in a range of other conditions such as hydrocephalus, cerebrovascular disease, primary progressive FOG (Fasano and others 2012) and the Parkinson-plus syndromes (Giladi and others 1997). Although there is little consensus, recent empirical insights gleaned from behavioral and neuroimaging experiments have provided a framework for the conceptualization of a common neural mechanism for freezing that is able to incorporate a wide range of clinical and behavioral characteristics associated with the symptom.

In this article, we will provide a brief overview of the neural control of gait, which consists of an evolutionary hierarchy that affords flexible, dynamic control over the movement of the lower limbs during changing sensory circumstances. We will then present evidence to suggest that all forms of freezing manifest in the brain via a common neural pathway, namely through the overwhelming inhibition of brainstem and thalamic motor nuclei by overactivity of the output nuclei of the basal ganglia (Lewis and Barker 2009; Shine and others 2013d). In doing so, we describe a theoretical framework of different triggers of behavioral freezing and then highlight future directions for studies that may hasten the discovery and development of novel diagnostic and therapeutic advances.

The Neural Control of Movement

Given the importance of locomotion in the adaptive survival of organisms, it is perhaps not surprising that the neural control of movement in humans involves wide range of interconnected circuitry across multiple levels of the nervous system, including the spinal cord, brainstem, basal ganglia, thalamus, and cerebral cortex (Takakusaki 2008; Takakusaki and others 2004) (Figure 1). Over evolutionary time, the systems that have developed to control coordinated limb movement have expanded

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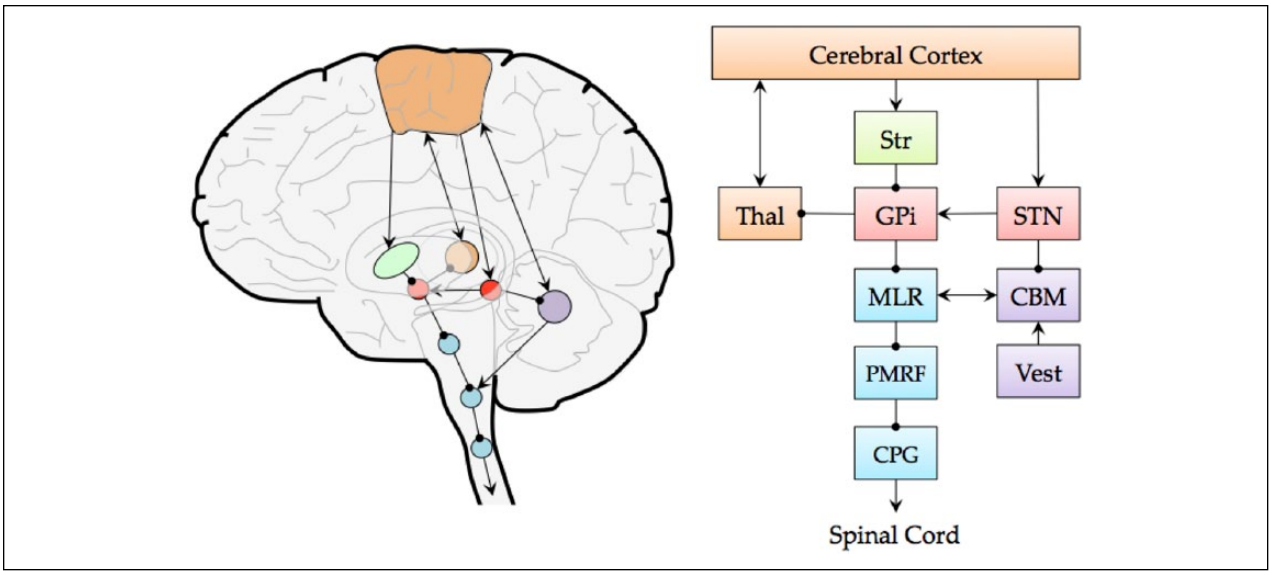

Figure 1. The neural control of gait. The effective control of gait is mediated by coordinated activity across multiple levels of the nervous system. The cerebral cortex and thalamus (shown in orange) maintain control over the brainstem structures that control gait (shown in blue), through connections with the basal ganglia nuclei (shown in green and red). The cerebellum (shown in purple) also has extensive connections with the vestibular system (purple), brainstem and striatum, effectively mediating the automatic processing of gait. CBM = cerebellum; CPG = central pattern generators; GPi = globus pallidus internus; MLR = mesencephalic locomotor region; PMRF = pontomedullary reticular formation; STN = subthalamic nucleus; Str = striatum; Thal = thalamus; Vest- vestibular nucleus; arrows = excitatory; circles = inhibitory.

hierarchically to involve higher order centers that allow for the behavioral control of more automatic functions within lower order systems. Despite working as a unified whole, these systems all display unique characteristics that define their involvement in complex, coordinated movement.

The lowest levels of the nervous system already contain a striking degree of complexity. Individual spinal cord segments receive a barrage of sensory signals from the large muscles of the lower limbs, which in turn create synaptic networks with interneurons that subsequently control the firing of associated muscle groups in both the ipsilateral and contralateral limb (Drew and others 2004). These circuits contain the capacity to coordinate spatio-temporal patterns of activation, particularly in response to changes in posture elicited by sudden shifts in gravitational force or other sensory challenges (MacKay-Lyons 2002). Importantly, these circuits are able to synchronize their activity without the need for supraspinal control, as evidenced by in vivo electrophysiological studies involving decerebrate cats and monkeys (Takakusaki and others 2003, 2004).

As neural systems increased in complexity over evolutionary time, separate systems emerged to ensure flexible and dynamic control over the relatively automatic neural reflexes of the spinal cord. These central pattern generators can be found at various levels of the spinal cord, however they are mostly concentrated in the medulla and pons of the brainstem (MacKay-Lyons 2002). Neural activity in these central pattern generators leads to coordinated firing of the circuitry present in spinal segments, leading to a wider range of potential movement patterns that are more easily manipulated in response to behavioral contingencies. For example, the mesencephalic locomotor region (MLR) of the brainstem is mainly involved in the production of movement, whereas the dorsal pedunculopontine nucleus (PPNd) is associated with the abrupt cessation of movement. Indeed, there is evidence to suggest that these structures may be organized into an inhibitory chain (Maloney and others 2000) (see Figure 2), affording flexible, cortical control over more ventral brainstem locomotor regions. The evolutionary advantage of these closely related systems is obvious in that it allows higher centers the capacity to abruptly shift the output of a complicated movement system in order to successfully achieve a particular goal.

The circuitry that has evolved to counteract gravity also plays an important role in tone, posture and gait. Consisting primarily of the semicircular canals, vestibular nuclei and cerebellum, this network of regions constantly monitors the dynamic relationship between our bodies and gravity, subtly adjusting muscle tone to maintain an upright posture (Seemungal 2014). This system is also integral for the initiation and maintenance of gait, controlling subtle yet precisely timed alterations

in posture and balance, known as anticipatory postural adjustments (or APAs), that release pressure on the foot prior to an initial footstep and during the swing phase of gait (Jacobs and Horak 2007).

The cerebellum also plays an important role in the dynamic coordination of muscle movements. Although the precise functional importance of the cerebellum is still a matter of contention, there is robust evidence to show that the cerebellum is involved in the coordination of complex spatiotemporal patterns of muscle firing (Ito 2008). This is particularly evident when movements have been overlearned due to excessive feedback from dopaminergic reward structures, such as the substantia nigra pars compacta (Bromberg-Martin and others 2010). The cerebral cortex appears to offer the opposite advantage to the movement system, allowing a wide variety of behavioral patterns to be deployed in a given context. In keeping with this concept, there is emerging evidence to suggest that the cortex and cerebellum work together to create a spectrum of behavioral capacities, ranging from entirely flexible at one end (driven mainly by cortical structures), to highly reproducible at the other (driven mainly by the cerebellum) (Doya 2000; Balsters and Ramnani 2011).

The aforementioned neural systems offer a great deal of behavioral flexibility in response to changing environmental contingency. However, they are effectively useless unless coupled with a system that affords control over their output. The basal ganglia nuclei, which consist of a series of highly interconnected nuclei in the telencephalon are ideally placed to execute this function. At rest, the main output structures of the basal ganglia (the globus pallidus internus [GPi] and the substantia nigra pars reticularis [SNr]) provide tonic GABAergic inhibitory tone over the brainstem structures that control gait (such as the MLR and PPNd) and the motor thalamus, effectively constraining information flow in the spinal cord and cortex, respectively. During activity, cortical input to the basal ganglia can either relieve (via the striatum) or facilitate (via the subthalamic nucleus [STN]) this inhibitory output. This allows flexible and volitional control over motor outputs, the execution for which can be effectively learned over the course of the lifespan.

To effectively mediate complex and rapidly changing external environments, a neural system controlling motor function also requires timely and appropriate feedback from the sensory environment surrounding the organism (Shergill and others 2013). Indeed, complex organisms utilize feedback from many qualitatively distinct sensory systems, including those that process visual, auditory and, most importantly, somatosensory information, to automatically respond to subtle changes in the external environment through a series of simple and complex reflex arcs (Nielsen 2003), effectively *embedding* the motor control system in whichever particular environment an organism learns to move. While the precise neural mechanisms underlying these functions are currently not clear, there is ample evidence to implicate many subcortical structures (such as the spinal cord (Nielsen 2003), superior colliculus (Gandhi and Katnani 2011), cerebellum (Koziol and others 2014) and thalamus (Murray and Wallace 2011)), along with more specialized circuits involved in specific sensory processing mechanisms, such as the lateral geniculate nucleus and the occipital cortex in the processing of vision (Milner and Goodale 1995), in the control of these capacities.

When working effectively in a hierarchical network, these circuitries can provide a seamless outflow of motor activity, exquisitely attuned to abrupt alterations in environmental contingency. However, failure of this system at multiple levels can manifest as paroxysmal impairments in gait maintenance or initiation, such as those experienced as FOG. In the following section, we will describe how the key clinical aspects of FOG impact on the different levels of this integrated system.

Pathological Impairment at Multiple Levels of Gait Control

Based on the hierarchical organization of this movement control system, pathological damage at different areas can manifest as strikingly different motor deficits. In most cases, these deficits are omnipresent, such as the hypertonic contractions following pyramidal neuron loss from a cerebrovascular accident. However, FOG is remarkable in that it is a distinctly paroxysmal phenomenon with a wide range of symptom severity and frequency across individuals with PD. As such, it is likely that pathological impairment at many different levels could manifest clinically as freezing. In keeping with this idea, freezing is known to occur in a range of disorders with contrasting neuropathologies targeting differing sites in the neuraxis. In the next section, we will highlight key empirical findings to clarify the likelihood that pathological damage at each level of the neural control of gait could potentially explain the pathophysiology of freezing in PD.

Given that the integration between sensory and motor signals first occurs in the spinal cord (Lemon 2008), it is possible that freezing arises due to impaired signaling within this system, leading to impairments in the coordination of agonist-antagonist interactions in the muscles of the lower limbs. However, results from empirical studies are in contrast with this hypothesis. For example, studies of muscle electromyography have shown that both of the major muscles of the lower limb

(the gastrocnemius and tibialis anterior) fire earlier than usual in the gait cycle during a freezing episode, however the dynamic reciprocal relationship between the two muscles is maintained (Nieuwboer and others 2004). This suggests that the pathological impairment in freezing occurs higher in the neural hierarchy, at the level of spatiotemporal gait control systems. In addition, freezing is commonly triggered by distinctly nonmotoric phenomena, such as dual-task conditions (Nutt and others 2011; Thevathasan and others 2012) or anxiety (Ehgoetz Martens and others 2014b; Lieberman 2006). As such, it is unlikely that isolated pathology within the spinal cord would manifest as freezing of gait.

Another potential target for freezing pathology lays in the more superior structures that control gait, such as the PPN and the MLR (Alam and others 2011; Pahapill and Lozano 2000) of the brainstem or the central pattern generators of the spinal cord (MacKay-Lyons 2002). These regions coordinate their activity to control complex spatiotemporal patterns of activity within more caudal spinal cord interneurons, effectively planning and executing gait activity in the presence of incoming sensory stimuli. Given that there are distinct cell populations within these regions that selectively activate or deactivate gait (Takakusaki and others 2003), it is perhaps not a surprise that these regions have long been highlighted as a potential pathological target for freezing of gait. Indeed, patients with progressive supranuclear palsy (PSP), a parkinsonian tauopathy, also experience severe FOG, and neuropathological evidence has shown that these patients have extensive damage within the PPN (Zweig and others 1987). However, patients with PSP suffer from a far more pervasive gait disturbance than those individuals with PD, with freezing events occurring in a much less paroxysmal fashion in the clinical setting. This clinical difference is likely due to the location of the PPN—direct pathological damage, as is the case in PSP, should manifest as a continuous gait disorder, whereas a functional impairment should manifest as a paroxysmal disorder. For these reasons, it is unlikely that freezing in PD is related to a complete lesion of the PPN and related structures, though it bears mention that damage to the area could easily play a contributing role to the condition (Lewis and Barker 2009). This interpretation is supported by the emerging role of low frequency deep brain stimulation of the PPN in the treatment of FOG (Alam and others 2012).

Freezing in PD has typically been shown to be at least partially responsive to dopaminergic therapy, implicating impairments within the basal ganglia, which are the most dopaminergically dense structures within the brain (Surmeier and others 2009). Indeed, these results could help to explain the variety triggers that can precipitate freezing given the widespread connections between the striatum and large regions of the cortex, which underlie a range of behavioral functions (Alexander and others 1986). However, studies exploring the response of freezing symptoms to dopaminergic administration rarely show a complete amelioration of freezing (Almeida and Lebold 2010; Shine and others 2013d). Indeed, there is some evidence to suggest that freezing may be exacerbated by dopaminergic medication in some individuals (Payne and others 2012). These results suggest that, similar to the brainstem, isolated dopaminergic depletion within the striatum is unlikely to fully explain the freezing phenomenon in PD.

There is also evidence to suggest that freezing may occur due to pathological impairments within the cortex. Indeed, many regions of the cortex are specialized for gait-related functions, including the volitional control of the lower limbs (precentral gyrus) (Graziano 2006), the execution of complex coordinated tasks (premotor and supplementary motor area) (Nachev and others 2008), the planning of gait movements (dorsolateral prefrontal cortex) (Stuss and Knight 2006) and the integration of visual information with ongoing gait alterations (presupplementary motor area) (Nachev and others 2008).

Lesions of the supplementary motor areas can manifest as freezing (Nachev and others 2008), perhaps because of an inability to integrate environmental changes with the dynamic flow of gait, a concept that is supported by results from both resting state (Fling and others 2013; Peterson and others 2014; Tessitore and others 2012) and functional (Shine and others 2013b, 2013c) neuroimaging studies. However, most patients with PD and freezing do not have obvious structural impairments in these medial frontal regions, suggesting that impairments within these cortical regions are likely functional in nature. Indeed, the few published studies reporting structural gray and white matter deficits in the brains of patients with freezing of gait offer little consistency, with results that are often lateralized (Fling and others 2013; Peterson and others 2014) and rarely show consensus across studies (Herman and others 2014; Snijders and others 2010). Once again, this highlights the notion that targeted pathology in any specific region of the brain is an unlikely unique candidate for explaining the pathophysiological mechanism of freezing in PD.

Recent research into freezing of gait has also highlighted the key role of abnormal sensory feedback in the manifestation of freezing behavior (Rocha and others 2014). It has been long known clinically that freezing of gait in PD is inextricably linked to changes in sensory input. For example, patients with the symptom are classically known to "freeze" in the doorway of their doctor's office. However, it has only recently been shown that these deficits may be due to impaired sensorimotor integration (Almeida and others 2002; Almeida and

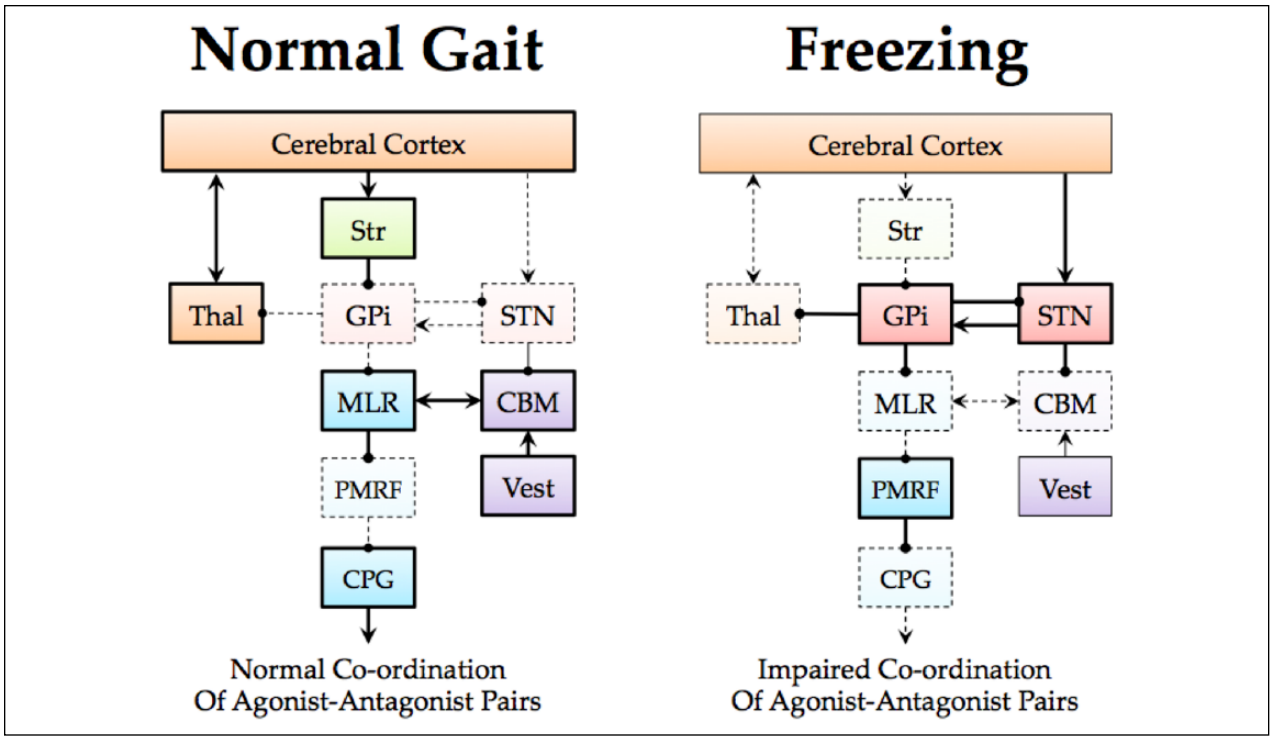

Figure 2. A comparison of normal gait and freezing. During normal gait (left panel), intact corticothalamic and corticostriatal systems lead to the inhibition of the output structures of the basal ganglia, allowing coordinated activity between the brainstem structures that control gait (shown in blue) and the cerebellovestibular balance system (shown in purple). During freezing of gait (right panel), impaired corticothalamic and corticostriatal systems lead to an increase in pallidal inhibitory outflow, which is often accentuated by glutamatergic input from the STN in the presence of increased response conflict, leading to the emergence of 5- to 7-Hz oscillations between the two nuclei. The STN activity also leads to impaired cerebellar output. Ultimately, the increased pallidal outflow manifests as impaired co-ordination of flexor-extensor pairs in the lower limbs. CBM = cerebellum; CPG = central pattern generator; GPi = globus pallidus internus; MLR = mesencephalic locomotor region; PMRF = pontomedullary reticular formation; STN = subthalamic nucleus; Str = striatum; Thal = thalamus; Vest – vestibular nucleus; arrows = excitatory; circles = inhibitory.

Lebold 2010; Ehgoetz Martens and others 2013a, 2013b, 2014a; Lebold and Almeida 2010) or visuospatial processing deficits (Nantel and others 2012; Vercruysse and others 2012a). Despite these insights, it is unclear at present whether these impairments are due to pathological impairment in the parietal cortex (Rubino and others 2014; Velu and others 2014), which controls the integration of complex sensory and motor signals (Harrison and others 2010), or in subcortical structures, such as the basal ganglia, thalamus, spinal cord and cerebellum, which control the more automatic processes associated with sensorimotor integration (Nielsen 2003; Koziol and others 2014).

Together, these studies highlight an important aspect of the pathophysiology of freezing of gait: a paroxysmal phenomenon is unlikely to be due to a focused, structural lesion. Rather, the disorder will most likely occur secondary to dysfunctions within a large neural system that can flexibly modulate the body's response to dynamic changes in environmental challenges. In the next section, we will outline a common neural mechanism for freezing that can account for the different aspects of the phenomenon, potentially highlighting novel targets for diagnosis and therapeutic intervention.

A Common Neural Mechanism for Freezing of Gait

There is now abundant evidence to demonstrate that stimulation of the output structures of the basal ganglia leads to GABAergic inhibition of the brainstem and thalamic structures that control gait, which ultimately manifests as akinesia (Takakusaki and others 2003). Of all basal ganglia output structures, the GPi and SNr provide the largest inhibitory afferent connections to these regions (Nambu 2004), suggesting that over activity in these nuclei exists as the final common link in freezing (Figure 2). Importantly, any neural circuitry that increases the firing rate of these nuclei would then, by definition, be implicated in freezing as well.

It is well known from models of the basal ganglia that the striatal nuclei provide inhibitory control over the GPi and SNr (Nambu 2004), effectively "releasing" the tonic GABAergic inhibition mediated by the output structures of the basal ganglia. As such, any hypoactivity within the striatum would therefore lead to a relative increase in inhibitory outflow from the basal ganglia (Lewis and Barker 2009). If the striatal efferents were lost entirely, however, this would theoretically lead to marked akinesia, as almost no output would be possible. This suggests that paroxysmal bouts of decreased striatal activity are responsible for individual freezing episodes, a conception that is supported by results from recent functional neuroimaging studies (Shine and others 2013b, 2013c; Vercruysse and others 2013). This idea is also able to explain the importance of neuronal integrity within the supplementary motor regions of the cortex, as these areas send excitatory glutamatergic efferents to the caudate nucleus within the striatum. Therefore, impaired signaling from these regions, either due to structural or functional dysfunction, could also lead to a relative level of inactivity within the striatum, allowing for concomitant increases within the GPi and SNr.

Freezing has been associated with a number of triggers, such as dual-task performance, anxiety, irregular cueing, and perceptual obstacles (Heremans and others 2012; Spildooren and others 2012; Vandenbossche and others 2012b). Although the normal processing of these triggers likely recruits unique patterns of neuronal circuitry, dysfunctional activity within each system is processed through a common neural pathway: namely, the STN (Cavanagh and others 2013; Shine and others 2013e). Whenever a neural region is unable to complete its' function in a timely manner, response conflict arises, leading to increased activity within the hyper-direct pathway of the basal ganglia, which links the pre–supplementary motor area and other areas of frontal cortex with the STN (Haynes and Haber 2013). The STN sends strong excitatory efferents to the GPi/SNr, which means that any increase in the firing rate of STN neurons leads directly to an increased firing rate within GPi/SNr GABAergic neurons, in turn inhibiting the PPN/MLR that will ultimately manifest as freezing (Shine and others 2013e). Importantly, this mechanism suggests that freezing is due to impairments in conflict processing *independent* of the processing system of which the conflict occurred. As such, the model can be just as effectively applied to freezing that occurs secondary to motor, cognitive, affective, or perceptual conflict.

Although sensory inputs can exacerbate freezing behavior, there is also ample evidence to suggest that in certain circumstances, appropriate patterns of sensory input can in fact alleviate the symptom (Nieuwboer 2008; Spildooren and others 2012; Vercruysse and others 2012b). For instance, the presence of horizontal lines on the ground in front a susceptible patient can cause a marked reduction in freezing behavior, presumably due to either improved motor planning secondary to an overt movement or perhaps due to the repetitive input of structured visual information (Nutt and others 2011). Similarly, regular auditory input via a metronome (Rochester and others 2009) or appropriate tactile input (Nieuwboer 2008) can also alleviate freezing. Viewed through our hypothetical model, these improvements in gait are likely due to systematic reduction in response conflict (Moustafa 2014; Shine and others 2013e; Vandenbossche and others 2012b), which would be decreased because of an overreliance on goal-directed behavior. In effect, this narrowing of focus would improve motor output due to a global refinement in action planning and execution. This interpretation is aligned with the known reduction in clinical benefit of external cueing over time, as subjects habituate to the novelty of the stimuli as the responses required become more automatic (Nieuwboer and others 2009; Vandenbossche and others 2012a).

The combination of impaired activity within the striatum and increased activity within the STN can also explain the presence of *trembling in place* where oscillatory movement at 5 to 7 Hz is observed in the lower limbs during a freeze (Moore and others 2008). The presence of trembling in place has been taken as a key clinical marker of FOG (Moore and others 2013; Nutt and others 2011) and has been utilized in a number of accelerometry studies. Evidence from computational studies (Frank 2006) has shown that in the absence of inhibitory striatal input, excitatory projections from the STN to the GPi leads to the emergence of 5- to 7-Hz oscillatory activity, presumably due to the inhibitory back-projections from the GPi to the STN (Bolam and others 2000). This emergent property of the basal ganglia circuitry would therefore manifest as tonic–clonic bursts of excitation and inhibition onto the PPN/MLR, which would then travel down the spinal cord to influence the musculature of the lower limbs to oscillate at the same frequency (5-7 Hz) (Moore and others 2008). Importantly, these transient increases in oscillatory inhibition would not necessarily be present at rest, at which time a global increase in oscillatory inhibition would be more likely to manifest as a general akinetic state (Galvan and Wichmann 2008).

The presence of increased contextual firing within the STN may also help explain a heretofore poorly understood aspect of freezing, namely the loss of automaticity. Many studies have demonstrated that patients with freezing perform poorly on tasks that require the coordinated manipulation of multimodal behavior (such as counting out loud backward while walking) (Spildooren and others 2010), suggesting a lack of automatic control

of gait and cognition in patients with FOG. Although the execution of these tasks likely requires coordination among multiple neural systems, the cerebellum has recently been shown to be instrumental for the automatic performance of overlearned tasks, such as gait across multiple behavioral domains (Balsters and Ramnani 2011). Interestingly, increases in excitatory output from the STN also reach the cerebellar cortex, via the pontine nuclei (Bostan and others 2013), whereby they could conceivably cause an overwhelming increase in inhibitory output on the deep cerebellar nuclei, which are the major output structures of the cerebellum (Ito 2006). Although this function is most likely adaptive in the healthy brain, in the context of impaired dopaminergic projection and other neural degeneration, any increases in conflict would ultimately lead to both akinesia *and* an inability to rely on previously learned habitual responses (see Figure 2). Alternatively, abnormal discharges from the deep cerebellar nuclei could also negatively interact with descending motor commands from both motor cortex and the basal ganglia, leading to impairments in gait, perhaps secondary to functional reorganization (Gilman and others 2010; Zwergal and others 2013) due to massive GABAergic pallidal inhibition (Lewis and Barker 2009). Although this mechanism is consistent with findings from structural neuroimaging studies (Fling and others 2014; Peterson and others 2014; Schweder and others 2010), further research into the functional capacities of these complex circuits is required before we can determine how targeted impairments in this region might manifest clinically.

Although we are proposing that freezing behavior manifests via a common final pathway—namely, overwhelming GABAergic inhibition of the brainstem structures controlling gait (Figure 2)—there is ample evidence to suggest that freezing can manifest in disorders with relative sparing of dopaminergic systems, suggesting that the basal ganglia need not be involved in freezing behavior. For instance, patients with cerebrovascular accidents affecting the supplementary motor regions of the cortex often display gait freezing (Hashimoto 2006). Similarly, experimental lesions of cholinergic projections to the frontal cortex in mice can also induce freezing-like behaviour (Kucinski and others 2013), a result consistent with recent positron emission tomography studies in human subjects with Parkinson's disease (Bohnen and others 2013, 2014). Although these two examples do not contain pathological impairment of the basal ganglia, it is likely that impairments in the timing of neuronal firing from supplementary motor regions would lead to underactivation of the striatum, and hence, overactivity of the globus pallidus. As such, despite occurring via distinctly different triggers to those displayed by subjects with Parkinson's disease (dopaminergic depletion of the striatum) or progressive supranuclear palsy (pathological impairment of the pedunculopontine nucleus), it is likely that freezing secondary to cortical pathology still manifests via the same common neural pathway.

Future Directions

Despite potential consensus regarding the pathophysiological mechanism of freezing of gait, a number of areas require further exploration before any firm conclusions can be made. For example, it is currently not clear why sensory cues can both exacerbate and alleviate freezing in patients with PD (Ehgoetz Martens and others, 2013a; Ito 2006). In addition, there is much to be explored regarding the role of timing in freezing, as subtle alterations in rhythmicity and spatiotemporal coordination can either provoke or relieve freezing. Indeed, recent work has even shown that chaotic cueing may improve gait parameters, albeit in healthy subjects (Hunt and others 2014). Furthermore, it is currently unclear whether balance impairments that often accompany freezing are part of the same or a related phenomenon (Jacobs and others 2009; Thevathasan and others 2012; Ehgoetz Martens and others 2013a).

Further studies utilizing advances in neuroimaging will also help to clarify the pathophysiological mechanism of freezing. For example, it is a direct prediction of this work that all freezing episodes should manifest via a common neural pathway; however, the precise circuitry leading up to episode will likely differ depending on the specific trigger that causes an episode. Functional neuroimaging using virtual reality (Jacobs and others 2009; Shine and others 2011, 2013b, 2013c, 2013d; Thevathasan and others 2012) or imagined walking (Shine and others 2011, 2013b, 2013c, 2013d; Snijders and others 2010) may help clarify this circuitry. These studies should also seek to test the hypothesis that freezing is because of impaired interhemispheric coordination (Plotnik and others 2005), a hypothesis that has received recent empirical support (Fling and others 2013, 2014; Peterson and others 2014), but requires clarification in future studies.

These same functional questions can also be addressed while directly recording from key subcortical structures, such as the STN and PPN, during deep brain stimulation surgery (Snijders and others 2010; Thevathasan and others 2012). Indeed, these investigations should clarify the hetereogeneous response of freezing to DBS surgery in the STN (Thevathasan and others 2012; Vercruysse and others 2014), which may be due at least in part to the marked heterogeneity between the different subdivisions of the STN (Hill and others 2012). Indeed, the targeted selection of specific subdivisions of the STN (Haynes

and Haber 2013) may potentially improve clinical outcomes from DBS. Similarly, the selection of alternative neural targets, such as the substantia nigra pars reticulate, which has been implicated in gait cessation (Chastan and others 2009), may also help improve the clinical efficacy of DBS for patients with freezing. Finally, the application of neurophysiological techniques with high temporal resolution, such as EEG (Shine and others 2013a; Vercruysse and others 2014), will help to further clarify the important role of timing in freezing.

An improved understanding of the situations that lead to increased neuronal conflict may also help clarify the pathophysiological mechanism of freezing. For example, it is a direct prediction of recent hypotheses (Giladi and others 1992; Lewis and Barker 2009; Nutt and others 2011; Shine and others 2013d; Vandenbossche and others 2012a) that improvements in global neural efficiency should alleviate FOG; however, the mechanisms of such efficiency are poorly understood in the brain. If these mechanisms are clarified in the general neuropsychological literature, they can perhaps be exploited to help train patients to avoid freezing, potentially via targeted cognitive training programs, or through the exploitation of emerging closed-loop deep brain stimulation technologies that can exploit dynamic alterations in oscillatory neuronal firing to alleviate paroxysmal symptoms. These studies may also help to decipher the role of anxiety in the exacerbation of freezing. Indeed, the detrimental effects of anxiety may in fact be due to systems-level impairments in neural reserve, a hypothesis that can be directly tested in future experiments.

The results of this targeted review also have implications for the therapeutic management of FOG. Indeed, our review suggests that the search for a single pathological target is unlikely to clarify the pathophysiology of freezing. Rather, multicenter trials could instead focus studies toward clarifying subtypes of freezing depending on the relative level of pathological damage to the different levels of the neural system (e.g. cortical, striatal, brainstem), perhaps reclassifying each patient by the degree to which each system is impaired.

Conclusion

The evidence presented within this manuscript suggests that freezing in PD is a heterogeneous symptom, but that a final common neural pathway defines the manifestation of the disorder. This conclusion predicts that there are no distinct "subtypes of freezing" but rather that different elements of pathological insult in the brain will cause a tendency for certain specific situations (such as walking through a narrow doorway or increased noradrenergic tone secondary to anxiety) to manifest as pathological activity within this common pathway. Future studies directly answering this question are of great importance, as they will help to define the next generation of therapeutic and diagnostic tools to aid in the treatment of this debilitating symptom.

Authors' Note

Simon J. G. Lewis and James M. Shine provided equal contributions to this article.

Declaration of Conflicting Interests

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

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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