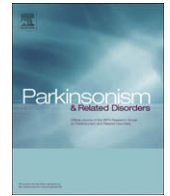




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## Parkinsonism and Related Disorders

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## Point of View

## A pathophysiological model of freezing of gait in Parkinson's disease

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## ARTICLE INFO

## Article history:

Received 15 June 2008

Received in revised form 11 August 2008

Accepted 19 August 2008

## Keywords:

Parkinson's disease

Freezing of gait

Synchronization

Oscillations

Basal ganglia

Motor

Cognitive

Limbic

## ABSTRACT

Freezing of gait (FOG) is a common phenomenon in Parkinson's disease (PD) affecting over half of those in the advanced stages of the disease and often does not respond to standard drug therapies. This article proposes a possible mechanism by which this disorder of movement comes about.

Co-ordinated neural activities are dependent on a series of parallel neuronal networks passing through the basal ganglia connecting and integrating functions. In healthy subjects, these competing, yet complementary, networks permit tight regulation in the broad domains of motor, cognitive, and limbic functions. In patients with PD, the loss of striatal dopamine coupled with the limited repertoire of the output nuclei within these pathways allows for an element of 'cross-talk' between competing inputs, which in turn could lead to a paroxysmal excessive inhibition of the thalamus and pedunculopontine nucleus triggering freezing of gait. It is further postulated that this phenomenon may be acting via a transient period of increased synchronization within the basal ganglia oscillations.

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## 1. Introduction

Parkinson's disease (PD) is a common neurodegenerative condition affecting around 1% of people over the age of 60 years. The disease has a major impact on the quality of life of these patients, their families and carers carrying a significant socio-economic burden, which has been estimated in a recent UK study to involve an annual healthcare cost of over £5000 per patient [1].

In addition to its motor aspects, PD is known to have profound effects on both memory and mood [2,3]. Quality of life is further impacted by a range of other complaints including pain, bowel dysfunction and disturbances of sleep [4].

Although symptomatic treatments are very helpful, particularly in the early stages of the disease, patients commonly develop specific late onset manifestations, which do not respond easily to medications. Disease progression is notably correlated with deterioration of gait and specifically the phenomenon of freezing of gait (FOG) where patients experience sudden unwanted arrests in their walking. During these freezing episodes, patients suddenly suffer an inability to move, often describing themselves as having been 'stuck to the floor'. Patients suffering with FOG are significantly more likely to experience falls [5] and are consequently more likely to require admission to a nursing home [6].

The basis for FOG remains unknown as it responds poorly to L-dopa therapy [7]. Furthermore, other treatment strategies such as deep brain stimulation [8], the use of the psychostimulant medication methylphenidate [9] and environmental cueing devices [10] have shown at best modest benefits. In this review, we have therefore attempted to take the current understanding of basal ganglia circuitry and explain FOG in relation to it with the hope that this will lead to new, testable hypotheses.

## 2. Characterisation of freezing

Freezing of gait is not unique to PD as it has been reported in a number of other conditions such as progressive supranuclear palsy (PSP), normal pressure hydrocephalus and vascular parkinsonism [11]. This finding indicates that the phenomenon is not uniquely related to severe dopamine depletion and suggests that the interruption of common neural networks along differing points by a variety of pathological mechanisms may result in the same symptomatic end point.

In the case of PD, there is a clear relationship between disease progression and FOG with over half of those patients in the advanced stages of disease experiencing this symptom [12] but it also affects L-dopa naïve patients who are in the earlier clinical stages [13,14]. This suggests that in PD the distribution of pathology rather than the absolute level of dopamine depletion may be the critical factor.

The concept of disease heterogeneity in PD is well represented in the literature [15–17] and is usually ascribed to specific temporal

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and spatial topographical patterns of neuronal loss [18,19]. In keeping with this it would appear that there is a correlation between the initially dominant symptom experienced by PD patients and their subsequent risk of developing FOG. Indeed, those patients who go on to develop FOG are more likely to have significant cognitive impairments and had initial symptoms of gait disturbance and rigidity rather than tremor [11–13], suggesting that such patients may have a unique pattern of pathology from disease onset.

### 3. Therapeutic approaches

Attempts to treat FOG have varied. One approach attempted to use botulinum toxin A injected into the calf muscles on the basis that the problem in this condition is akin to that seen in dystonia. Whilst an initial open-label study showed some promising symptomatic benefits [20], a subsequent randomized double-blind placebo-controlled crossover study showed no such benefits [21].

Other strategies have involved using treatments that ameliorate the dopaminergic loss and its downstream effects within the basal ganglia circuitry. Thus L-dopa has been tried with only limited success [7]. Indeed, one study revealed that L-dopa could significantly reduce episodes of FOG but this improvement was not correlated with the alleviation of bradykinesia, rigidity or poor balance [22]. This finding suggests that FOG is mediated by a different motor pathway to that underlying these features of PD (see below).

Alternative drug treatments have been evaluated such as the psychostimulant medication methylphenidate (MPH) and one recent study has demonstrated a significant reduction in the frequency of FOG episodes following a three-month exposure to MPH in a group of PD patients who were previously on optimal medical management [9].

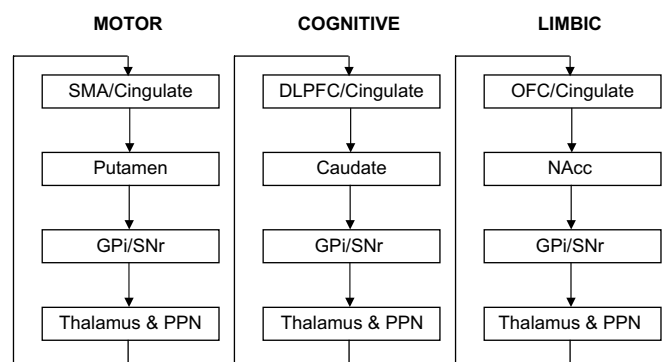
Thus whilst abnormalities in dopaminergic pathways may be linked to FOG, it is clear that other non-dopaminergic pathways or structures must lie in the pathogenic pathway. In recent years, the surgical management of PD has emerged with the subthalamic nucleus (STN) being the preferred target site for deep brain stimulation (DBS). Using this approach, it has been shown that bilateral STN stimulation can lead to a significant improvement of FOG in patients during their 'Off' phase (when motoric symptoms are not suitably relieved) but does not necessarily improve this symptom during their 'On' period [8]. However, other authors have demonstrated that although the majority of patients with dopamine responsive FOG derive an improvement with STN stimulation, this is not as effective as the response to L-dopa and indeed a number of patients undergoing DBS went on to develop gait disturbances for the first time only after the procedure [23]. Attempts to correlate the effects of DBS on FOG utilising functional neuroimaging have revealed a disseminated neural network operating through parietal, occipital and temporal sensory association cortices [24]. A recent study suggests that 'On' period gait disturbances can be more reliably improved in patients who have undergone a combination of bilateral stimulation of the STN and the pedunculopontine nucleus (PPN) suggesting that both basal ganglia and brainstem locomotor nuclei are implicated in the genesis of this symptom and may play a major role in FOG [25].

### 4. Basal ganglia circuits

As stated above, disturbances in basal ganglia circuitry play a central role in the pathology of PD. It is well described that co-ordinated neural activities are dependent on a series of parallel neuronal networks passing through the basal ganglia connecting and integrating functions between the basal ganglia nuclei, various regions of the cerebral cortex, the thalamus and brainstem [26],

although more recent work showing the dense arborisation of connections between basal ganglia nuclei would challenge this model as simplistic (for review, see Ref. [27]). Through their structural convergence and functional integration, these segregated circuits allow processing of diverse inputs within, rather than between, each of the identified circuits and permit tight regulation in the broad domains of motor, cognitive, and limbic functions (Fig. 1 adapted from DeLong and Wichmann [28]). The dynamic balance of dopaminergic stimulation exerted via these competing, yet complementary, pathways is central in determining behavioural outcomes (for review, see Ref. [28]).

The best characteristic of these pathways is the motor loop subserving motoric function. In PD, the natural balance within the motor loop is lost owing to the depletion of dopamine in the striatum. This loss of dopaminergic stimulation results in an over-activation of the GPi/SNr output nuclei causing a profound inhibition on both the thalamus and PPN, which in turn impairs both ascending and descending pathways resulting in the reduction of motor activity. Thus, this model of the motor loop in the basal ganglia networks allows a pathophysiological explanation of the akinetic features of disease and is well supported by evidence from biochemical, electrophysiological, functional imaging and clinical studies [29–33]. However, as already stated this feature of PD does not necessarily correlate with FOG suggesting the involvement of additional non-dopaminergic pathways and/or structures. One such structure is the PPN and clinicopathological studies undertaken in PD patients have identified that cellular loss within the PPN can be correlated with disease progression and gait disturbance [34–36]. This finding suggests that cellular degeneration in this region may act synergistically with nigrostriatal cell loss to explain aspects of gait failure in the disease, and also might explain the relative and partial resistance of such symptoms to respond to dopaminergic amelioration. Interestingly, utilising the technique of DBS to target the PPN has revealed a range of clinical responses critically dependent on the frequency of stimulation [37–39]. At higher frequencies (75 Hz), gait performance including freezing episodes is seen to deteriorate, whereas in the same patients, improvements were seen when the DBS was set at a lower firing frequency (20 Hz). This suggests a critical role for the PPN in modulating gait, a fact reinforced by the recent finding that combined DBS of the STN and PPN bilaterally resulted in gait improvements over those seen when just STN stimulation has been employed [25]. Such electrophysiological evidence for the key role of the PPN in gait is supplemented by pharmacological work performed in a primate model of PD [40]. This study demonstrated the



**Fig. 1.** (Adapted from DeLong [28]) This parallel series of segregated pathways allows the functional integration of information from a diverse range of inputs and modulates appropriate responses. SMA, supplementary motor area; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; Cingulate, Cingulate cortex; NAcc, nucleus accumbens; GPi, globus pallidus, internal segment; SNr, substantia nigra pars reticulata; PPN, pedunculopontine nucleus.

positive benefits in locomotor function following GABA antagonism at the level of the PPN in non-human primates that had been rendered parkinsonian secondary to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) lesioning. Thus it seems likely that PPN pathology in PD acts in series with the dopaminergic loss in causing gait disturbance.

## 5. Mechanisms underlying freezing

We have suggested the anatomical pathway and the key structures in it, but how does FOG come about? Despite the predominance of motoric symptoms in PD both cognitive and limbic deficits are well recognised [2,41–44]. The observation that freezing symptoms in PD patients are responsive to external stimuli has long been recognised. Many patients and their carers are well aware of simple ‘tricks’ to alleviate their freezing attacks, such as stepping over a small obstacle (like a foot) to recommence walking. However, attempts to improve FOG using environmental cueing have yielded disappointing results with one recent study, which used a program of cueing training in the home demonstrating benefits with regard to gait and freezing that were at best modest and tended to wear off rapidly over six weeks [10]. Such studies do show some promise and their apparent limitations may relate to the intensity and dosing schedule of the training program employed. Furthermore, targeting particular aspects of movement, such as the impaired judgement of amplitude that has been demonstrated in PD, may offer potential useful strategies [45].

Whilst FOG in PD represents the most common form of motor arrest or motor block seen within the condition, other forms of motor block are well recognised and can occur during handwriting, rapid alternating hand movements such as when brushing teeth and as speech arrest. Such examples of motor blocking suggest that freezing *per se* is not inextricably linked with the processes of locomotion but rather there is a specific topographical element to it. Furthermore, freezing episodes can be brought on by both environmental stimuli and cognitive load [46]. Provocative environments, commonly observed when patients approach narrow doorways or need to change direction, can often precipitate freezing episodes. Similarly, patients experience an increased tendency towards freezing when they are required to deal simultaneously with an increased cognitive load, such as trying to hold a conversation whilst walking along. It is possible that the heightened freezing behaviour observed in these situations is the result of an impaired ability in these patients to successfully accommodate different motor tasks ‘on-line’, as has been previously shown in studies of PD highlighting problems in trying to undertake more than one motor task simultaneously [47]. Similar difficulties have been observed in PD patients on cognitive testing paradigms investigating their ability to mentally shift between stimuli [48–50], raising the possibility of a close inter-relationship between the neural circuitry disturbances underlying both physical and cognitive freezing.

Cognitive deficits in PD can be divided into two patterns, which broadly correlate with differing pathological substrates. Neuropsychological tasks with a more posterior cortical basis appear to be predictors for the development of frank dementia in PD and are most likely to be correlated with the diffuse accumulation of Lewy body pathology [51]. More subtle cognitive deficits are common, even in the earlier clinical stages of the disease, and have their most significant impact on executive processes such as working memory, planning and attentional set shifting (for example, Refs. [48,52]). There is good evidence provided by clinicopathological [19,53], animal [54] and neuroimaging studies [55–57] to suggest that the dopaminergic projections involved in cognitive function project to both the caudate nucleus and prefrontal cortex. Analogous to the motor loop disturbances seen in PD, it has been proposed that

dynamic dopaminergic changes, predominantly at the level of the caudate nucleus within this system, lead to inefficient processing whilst performing dependent cognitive tasks that ultimately manifest with a reduced behavioural performance (for review, see Ref. [58]). The level of cortical dopamine relative to the striatum and also non-dopaminergic pathways will further impact upon these processes.

The limbic loop of the basal ganglia circuitry is responsible for the regulation and control of behaviours underlying motivation, decision-making and goal-directed reward. Afferent projections from a wide range of cortical areas (including the orbitofrontal, cingulate and hippocampal formations) and sub-cortical structures (amygdala and ventral tegmental area) target the ventral striatum, which is composed of the ventromedial part of the caudate nucleus and putamen along with the nucleus accumbens (NAcc) and olfactory tubercle. Within the NAcc, these inputs are integrated under the modulatory influence of dopamine (for review, Ref. [59]). Efferent projections from this structure again target the major output nuclei (GPi/SNr) of the basal ganglia allowing integration of circuitry sub-serving differing functional modalities to translate limbic ‘drives’ into motoric actions (Fig. 1).

The mechanisms by which disturbances in these functional pathways translate into deficits at a neuronal level are not fully understood but studies in rodents, non-human primates and latterly PD patients undergoing DBS have begun to reveal the abnormalities in neural networks that may be important [60]. These studies have shown that under normal conditions, neighbouring cell populations within the basal ganglia nuclei fire asynchronously. By comparison, significant synchrony is observed in the dopamine depleted state, typically recorded at a frequency of between 8 and 30 Hz (known as the ‘broad beta frequency band’) [60]. Treatment with dopaminergic drugs reduces synchrony and this can be further correlated with the alleviation of bradykinesia and rigidity in these patients [61]. Thus, the induction of asynchrony seems important in mediating the beneficial effects of L-dopa therapy and DBS on PD akinesia/rigidity. The situation regarding FOG remains unresolved although as stated before, such therapies are less effective in treating FOG.

Levels of synchronization have also been found to correlate with sensory stimulation and cognitive processing. In primate studies, striatal neurones use sensory stimuli in relation to events, as cues to prepare for the performance of tasks [62] and similarly synchrony is reduced in PD patients just before and during self and externally paced voluntary movements [63]. It is not known whether the level of synchronization within the basal ganglia circuitry represents a linear function of the striatal dopamine level and it has been suggested that at some critical point, the number of synchronous neurons in the basal ganglia network could increase exponentially [64]. Thus, FOG may be due to a different type of synchrony in terms of its frequency, range and network that is triggered by sensory inputs along with cognitive and limbic processes. A role for the PPN in such a system would need to be accommodated in any such model of FOG.

## 6. The proposed model

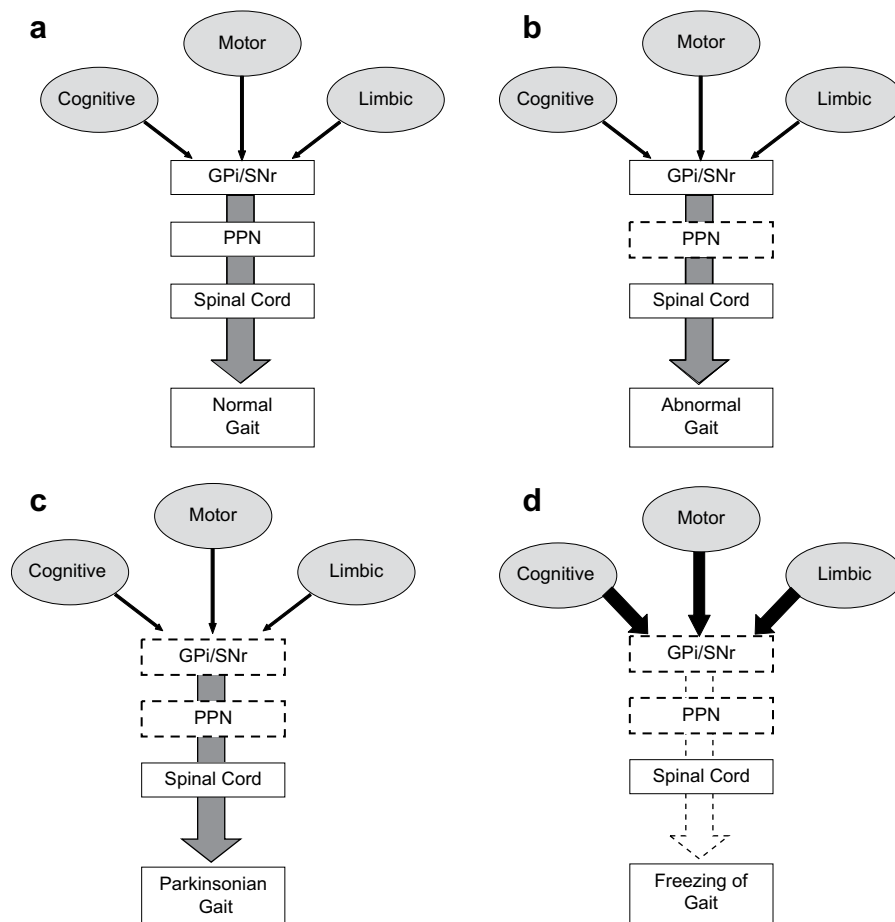
In healthy subjects, the basal ganglia circuits operate through a series of parallel pathways that can integrate information from a wide range of diverse inputs and co-ordinate an efficient functional output such that, individual disease features can be attributed to deficits in specific pathways. Most notably with regard to FOG in PD, a breakdown in the normal operation of the motor loop results in an inhibition of the PPN, an area with descending connections to the spinal cord and presumed central pattern generators. Stimulation of the PPN has been shown to elicit stepping movements in decerebrate animals, underlining the crucial

importance of this structure in the mechanisms underlying locomotion [65,66]. However, the observation in patients that FOG can be both provoked and relieved by cognitive and limbic features suggests the involvement of other pathways in addition to the motor loop.

Normal gait is dependent on processing within both cortical and sub-cortical regions (Fig. 2a) and the evidence presented suggests a critical role for the PPN in regulating the outflow of these processes in human locomotion. Furthermore, any insult to the integrity of this structure would provide a non-dopaminergic mechanism to explain disturbances in gait (Fig. 2b). Disruption at this level may also offer an explanation for the phenomenon of FOG in patients with other causes of parkinsonism and indeed it is possible that pathological changes targeting this region in PD may account for those patients who develop this symptom in early disease. It is also clear that the output nuclei of the basal ganglia circuitry have a profound effect on determining the level of activation within the PPN and in combination this will clinically manifest as a parkinsonian gait (Fig. 2c). Furthermore, we propose that in PD, a paroxysmal deactivation of the PPN by reversible periods of over-activity in the GPi/SNr trigger episodes of FOG (Fig. 2d).

As stated, the limited repertoire of the output nuclei within the motor, cognitive and limbic pathways, which all target the GPi/SNr, allow for an element of ‘cross-talk’ between competing inputs.

Thus, in PD patients where striatal dopamine levels are reduced there may only be sufficient ‘reserve’ of neurotransmitter to accomplish limited tasks. In a simplified scenario striatal dopamine, already compromised in the region of the putamen, may be at a sufficient level to facilitate a parkinsonian gait. At this point, despite dopaminergic depletion the activation within the direct and deactivation of the indirect pathways would be sufficient to maintain a level of inactivation of the GPi that would facilitate movement (Fig. 2c). However, with the additional demands of a cognitive challenge or sensory overload from visual and other stimuli, the depleted nigrostriatal delivery of dopamine in the region of the caudate would lead to an under-activation of the direct and an over-activation of the indirect pathways. This would result in over-activity in the GPi and inhibition of the PPN and thalamus, resulting in FOG (Fig. 2d). Similarly, as patients are walking through a stimulating environment, they will be subject to increased limbic demands and sensory demands. It is well recognised that episodes of FOG are often exacerbated by attempting to walk through unfamiliar surroundings. It is clear that successfully negotiating a stimulus rich environment would rely on increased sensory information and limbic activity regulating a number of diverse processes. These limbic demands, operating via a depleted dopamine neurotransmitter system could also result in an over-activity of the GPi, thus inhibiting movement (Fig. 2d), which is further compounded by areas of intense sensory stimulation, such



**Fig. 2.** a) In the healthy state, neural activation within the cortex and basal ganglia circuitry facilitates PPN output to allow normal gait. b) It is clear that pathology centered on the PPN, such as non-dopaminergic neuronal loss, could interfere independently with normal gait processes. c) In PD, the significant loss of dopamine in the striatum results in the over-activity of the output nuclei of the basal ganglia (GPi/SNr), which in turn inhibits the already disordered PPN leading to a parkinsonian gait. d) The anatomical convergence and functional integration of the segregated motor, cognitive and limbic circuits on the GPi/SNr could lead to excessive paroxysmal inhibition of the PPN triggering freezing episodes under situations of information overload – sensory and/or cognitive. Furthermore, susceptibility to this phenomenon will be increased in patients where the integrity of the PPN is already compromised by local non-dopaminergic processes.

as approaching a doorway. In this model, there is a failure in attributing salience to a relevant sensory cue required for movement thus 'jamming' the system and leading to FOG. When patients who have experienced a freezing episode then focus on one external stimulus, such as stepping over a line, they suspend their performance of additional cognitive and limbic processes. This course of action reduces the degree of over-activation in the GPI allowing the basal ganglia circuitry to be 'reset', once again facilitating movement (Fig. 2c). Such an explanation could also account for the problems with multi-tasking and 'motor set' that have long been recognised in PD often in domains other than gait [47].

## 7. Underlying pathogenesis

In the model of FOG proposed above, paroxysmal excessive inhibition of the thalamus and PPN could result from a specific and transient local unavailability of dopamine due to 'competing' functional circuits. How this 'local shortfall' in the circuitry is translated into the disruption of motor sequences remains unclear but one explanation would be to suggest that these transitory conditions could result in a non-sustained period of increased synchronicity triggering a freezing episode. In this model, it is possible that environmental cueing acts to promote desynchronization allowing the circuitry to become reset by channelling information through a specific preserved pathway, which acts to reset the network. This proposed model would also be supported by the finding that FOG is correlated with disease progression where there is a reducing reserve of dopamine in the circuitry. Furthermore, non-dopaminergic pathology within the PPN may increase susceptibility to FOG according to the proposed model and may account for patients who do not respond fully to L-dopa and those who appear symptomatically to have less dopaminergic depletion. Indeed, such pathology may also account for the characteristic phenotypic features found in these patients. Namely, their dominant symptoms of rigidity at disease onset and cognitive impairments may represent manifestations of a more diffuse disease process, which involves a range of cortical and sub-cortical structures from disease onset.

## 8. Previous research

Although attempts at understanding the processes underlying FOG in PD have focussed on neurophysiological [67,68] and kinematic aspects [69], some limited attempts to look at this with functional imaging have been undertaken. Two studies have been performed in patients with FOG utilising the technique of single photon emission computed tomography (SPECT) to assess cortical perfusion. Although no significant deficits were recorded in one of these experiments [70], the other did demonstrate hypoperfusion in the orbitofrontal cortex of patients with FOG suggesting a possible role for this region in attacks of freezing [71]. One further study employed positron emission tomography (PET) to explore the levels of dopaminergic uptake and glucose metabolism within the basal ganglia [72] and demonstrated decreased dopamine uptake in both the putamen and caudate in patients with FOG. This method of analysis also revealed that glucose metabolism was increased in the putamen and decreased in the caudate within this patient group. However, the region of interest analysis looking at these changes failed to confirm any significant differences between patients with FOG and those without.

## 9. Conclusion

Whilst the proposed model attempts to account for our current understanding of the phenomenon of freezing, it is clearly simplistic and generalised. Testing this hypothesis of FOG is now

required. It is anticipated that directed studies in which cognitive and limbic load might be manipulated within behavioural, neuro-physiological and functional neuroimaging approaches will help determine their measurable effect on freezing behaviour. It is hoped that such studies will ultimately be combined with clinico-pathological correlations to help determine the utility of this proposed model.

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