Advances in our Understanding of the Brain Mechanisms of Freezing of Gait in Parkinson’s Disease

Freezing of gait (FOG) is a devastating symptom that affects the majority of patients with advanced Parkinson’s disease (PD). It typically manifests as a sudden inability to move the lower limbs despite the intention to walk. However, the phenomenon is not limited to gait and individuals with PD have been shown to suffer from freezing in other movements, such as handwriting, brushing teeth and even speech. The pathophysiology underlying freezing is not well understood but a number of recent research approaches have led to insights that offer the prospect of new avenues for therapeutic intervention and management.

Due to the obvious problems associated with the neuroimaging of gait disorders, the investigation of the neural basis of FOG has been problematic. Although potentially very informative, studies usually suffer from limits in temporal precision (such as Positron Emission Tomography) or are required to provide challenging links between imaging results and behaviour (such as tasks that measure brain activity while subjects watch a first-person perspective video of an actor walking). To combat these issues, a novel Virtual Reality (VR) paradigm in which subjects navigate a non-immersive, yet realistic three-dimensional environment using footpedals to control their ‘walking’ has been developed. The VR task requires bipedal motor activity whilst processing cognitive and environmental information. Importantly, the task can successfully and safely be performed with concomitant decreases in activity within the striatum, a key region in the basal ganglia nuclei. A subsequent study has demonstrated that these cortical and subcortical structures communicate well during effective navigation of the VR task, however when a subject shows evidence of a breakdown in the normal footstep pattern, their corticostriatal networks show a similar breakdown in effective communication. Together, these imaging studies provide convincing evidence that the dynamic process of freezing is due to paroxysmal breakdowns in communication between large-scale networks within the brain.

The results from these fMRI studies are also supported by recent evidence obtained from an ambulatory electroencephalography (EEG) study in which the electrophysiological correlates of brain activity have been measured whilst patients with FOG navigated a standardised clinical walking assessment (timed up-and-go). After strict correction for movement-related artefacts, it has been shown that episodes of freezing were associated with an increase in theta band power (~3-7Hz) over the central and frontal regions, which broadly map to motor execution and planning regions of the brain, respectively. In addition, there was a transition in the degree of synchrony between different regions in the theta frequency over the temporal evolution of a freezing episode, further supporting the notion that FOG is due to impaired functional coupling between distant brain regions.

Using these objective insights has led to a revised framework that extends a previously proposed model of freezing behaviour, in which freezing behaviour was conceptualised as occurring secondary to transient increases in GABAergic neuronal activity within the output structures of the basal ganglia (such as the globus pallidus internus), which ultimately manifests as an overwhelming inhibition of the key targets of the basal ganglia, such as the anterior thalamus and the brainstem structures controlling gait. Although the previous model made specific predictions regarding the likely behavioural predictions of freezing behaviour, the recent insights gained from the aforementioned neuroimaging and neurophysiological studies have helped to clarify the role of impaired corticostriatal coupling in the pathophysiological manifestation of FOG. For example, there is now evidence to suggest that impairments in neural coupling may precede freezing, providing a potential therapeutic avenue.

In addition, the neuroimaging studies above have also provided clues that help to link the impaired corticostriatal coupling to the final manifestation of freezing, which is most likely related to increased firing within the output structures of the basal ganglia. These results implicate dysfunction within the ‘hyper-direct’ pathway of the basal ganglia, which links regions of the medial frontal cortex (such as the pre-supplementary motor area or pSMA) with the subthalamic nucleus of the basal ganglia. Through its connection to the pSMA, the STN is able to bypass the striatum and directly drive an increase in inhibitory GABAergic output from

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The output structures of the basal ganglia, such as the internal segment of the globus pallidus (GPi), increased activity in the GPi, which is a member of the direct pathway of the basal ganglia, leads to an increase in the rate of inhibitory output onto the brainstem and thalamic structures that control the output of effective motor behaviours, leading to an increase in the inhibitory output of the basal ganglia. 1 This neural change represents as overwhelming inhibitory outflow onto the anterior thalamus (Thal) and the pedunculopontine nucleus (PPN), leading to decreased corticothalamic and brainstem activity, respectively, ultimately manifesting as freezing.

These proposed roles of the STN are well supported by both behavioural and neuroimaging evidence. For example, the STN has been consistently implicated in set-shifting behaviour, which has been shown to be impaired in patients with freezing. Furthermore, the role of the STN in freezing is aligned with the previously described functional neuroimaging studies that showed evidence that the globus pallidus and the STN enter into a low energy oscillatory state during freezing behaviour.

These new insights into the pathophysiological mechanism of freezing behaviour suggest a number of exciting directions for future studies. For instance, the VR task could be combined with direct cellular recordings during deep brain stimulation surgery to test the hypothetical prediction that freezing is associated with increased firing within the STN. In addition, the combination of these insights with the temporal predictive capacity of EEG could also potentially inform future therapeutics, perhaps utilising specific neurophysiological signatures to tune a closed loop deep brain stimulation feedback system that might even offer the potential of aborting freezing episodes.

**REFERENCES**