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Cognitive impact on freezing of gait in Parkinson's disease

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Abstract

Gait is a high-level locomotion pattern peculiar to humans. Human gait is controlled either voluntarily or automatically, the latter with very little attention to the task. In fact, both are probably involved continually to a varying degree in daily locomotion. The central control mechanisms of human gait remain unclear. It is generally believed that, while certain subcortical structures, such as the pedunculopontine nuclei and the basal ganglia, play important roles in automatic walking, the cerebral cortex also becomes involved due to changes in the level of effort and attention demands. Is freezing of gait (FOG) in Parkinson's disease (PD) affected by the level of automatic or voluntary control? Another factor may be a crucial key in determining the underlying pathological mechanisms of FOG in PD. Clarifying the degree to which the central nervous system's control of gait is involved in FOG in Parkinson's disease may reveal its underlying mechanism.

Keywords: Gait; Freezing; Cognitive function

1. Pathophysiology of freezing of gait (FOG)

This section describes output disorders and abnormal rhythm formation in voluntary movement. These motor problems may be the underlying physiological cause of the freezing phenomenon.

1.1. Output disorders in involuntary movement

Bradykinesia, which is a main symptom of Parkinson's disease (PD), has been regarded as a specific abnormality of the motor output system. It is an important symptom that cannot be separated from the freezing phenomenon. Bradykinesia has been studied using the reaction time paradigm and the target tracking method as pathophysiological indicators. In many cases, the reaction time paradigm has been applied to the arms or fingers. However, if the reaction time paradigm is applied for studying the pathophysiological relation to FOG, it is more appropriate to use the reaction time of the foot. Yanagisawa et al. [1] used dorsiflexion to elucidate this relationship. They showed a relationship between the delay in the reaction time and the severity of the disease (according to the Hoehn and Yahr's stage) in patients with PD. Furthermore, when comparing the presence or absence of a warning signal prior to the reaction, the presence of a warning signal was associated with a shorter reaction time in patients with severe symptoms. On the contrary, there was no difference between patients with mild symptoms and normal subjects. Thus, a warning signal significantly improves the reaction time in parkinsonian patients with severe symptoms. This indicates that reduced attention may be an essential characteristic of the disease. Auditory signals markedly improve FOG, suggesting that the attention system may be involved at the beginning of voluntary movement in PD.

Patients with PD often have difficulty executing ballistic movement. The physiological findings for this phenomenon are as follows. Firstly, parkinsonian patients are unable to voluntarily produce a large amount of force at the beginning of a ballistic movement.

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Secondly, patients with PD cannot form the normal pattern in which the larger the output for a simple movement task with varying outputs, the quicker the movement. These two findings may represent the same phenomenon. Schmidt et al. [2] proposed a pulse step model in which, for a simple ballistic movement, only the force for motor output changes regularly. Yanagisawa et al. [1] investigated ballistic movements using ankle dorsiflexion, in which subjects were required to execute voluntary isometric contractions that required various degrees of output. Yanagisawa demonstrated that normal subjects achieved a target once within the required time regardless of the degree of output. Alternatively, the parkinsonian group required increasingly longer periods of time, as larger outputs were demanded. Moreover, the outputs were step-like and the initial outputs were uniformly constant regardless of the required degree of force. These findings suggest that unitary outputs exists in PD. The unitary outputs are considered to result from lost synchronization of a large number of motor units. Yanagisawa et al. [1] regarded unitary outputs as the common pathophysiological basis in cog-wheel rigidity and freezing. As soon as a parkinsonian patient is freezing, movement is impossible, despite the patient's utmost effort. This FOG phenomenon may be explained by the theory of unitary outputs where a large number of motor units, required to overcome freezing, cannot be simultaneously employed.

1.2. Defective rhythmic formation

During daily activities of patients with PD, festination is frequently observed simultaneously with FOG. This phenomenon comprises the stuttering that can occur when speaking rapidly at a low tone, micrographia, difficulty in performing rapid and repetitive actions such as brushing the teeth, pulsion walking, and frozen gait, etc. Nakamura et al. [3] assumed a rhythm defect as the pathophysiology of such freezing with festination. They studied the phenomenon using the finger tapping method. The results showed that repetitive movements converge into a rhythm at a frequency of 4–5 Hz, which is equivalent to that of resting tremor in PD. This reasonably accounts for the freezing phenomenon observed in the repetition of a single movement in daily life.

What mechanisms cause freezing when performing complicated repetitive movements, such as utterance or writing? And how can one explain the contradictory phenomena of freezing and festination? Freund [4,5] explains that all voluntary movements are conducted at an appropriate rhythm that corresponds to the movements and range from 0 to ~8 Hz. In normal subjects, the maximum frequency is 8–10 Hz, which corresponds to the frequency of physiological tremors. In PD and cerebellar ataxia, the maximum frequency is limited to 4–5 Hz, which corresponds to that of tremors, and movements requiring quicker rhythms, such as writing or dealing with an eraser, cannot be executed. On the contrary, normal subjects usually process slow movements at a frequency of 2 Hz or less using a variety of sensory feedback mechanisms. In patients with PD, however, the rhythm speeds up, approaching the frequency of the parkinsonian tremor, which may result in festination. Rhythms are necessary to perform smooth movements, even those that are natural and non-repetitive. Thus, Freund's idea that various rhythms underlie daily movements is unique, and important, when considering freezing and festination.

Ueno et al. [6] studied FOG using floor reaction forces and surface electromyography. They developed several ideas regarding the rhythm defect associated with the freezing phenomenon. In their study, the rhythm of short-step walking was determined to be 0.9 ± 0.3 Hz in patients with PD and 1.5 ± 0.3 Hz in patients with vascular parkinsonisms caused by multiple lacunar infarction in the frontal cortex and the basal nuclei. There is no significant difference between the two frequencies. FOG, however, apparently has different rhythms, 4.6 ± 0.8 in patients with PD and 2.3 ± 0.6 in patients with vascular parkinsonisms. Both rhythms are faster than the normal gait of ~1 Hz. This gait speed prevents the subject from putting all their weight on one leg, preventing them from moving forward. Significantly, the rhythm of FOG is consistent with that of resting tremor in PD. While patients with vascular parkinsonisms rarely exhibit resting tremor, it is notable that the rhythms of frozen gait in both diseases differ, and that FOG shows the same rhythm as the resting tremor in PD.

What is the relationship between freezing and resting tremor in PD? In PD, resting tremors disappear when they initiate an action, however, these tremors become stronger under psychological stress, such as when doing mental arithmetic. However, resting tremors become prominent when the patient is walking. Resting tremors tend to appear prior to the beginning of movement, suggesting the preponderance of a central nervous system controlling and regulating the rhythms. Sudden freezing while walking may be manifested by a somewhat internally abnormal rhythmic formation that approaches the rhythm of resting tremor. This type of FOG is known as motor block [7]. However, external guides may suppress the occurrence of defective rhythms. For example, external pacing cues, such as the rhythm of a metronome or a pattern of horizontal lines, can prevent parkinsonian patients from sudden freezing while walking.

Freezing does not exactly correspond to resting tremors. Resting tremors disappear when the activation of dopaminergic neurons is accentuated by