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Neuroimaging of standing and walking: Special emphasis on Parkinsonian gait

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Abstract

Quadruped animal studies indicate two major systems for locomotion, the basal ganglia–brainstem and basal ganglia–thalamocortical systems. Consistent with these studies, human neuroimaging studies have suggested gait-related activity in the brainstem locomotor centers, cerebellum, basal ganglia, and multiple motor cortices. As for pathophysiology of Parkinsonian gait, underactivity of the supplementary motor areas and cerebellar hemisphere, combined with overactivity of the vermis, have been shown. Overactivation of the lateral premotor cortex is observed during paradoxical improvement of Parkinsonian gait under visual guidance. The activation of visuomotor network including the lateral premotor cortex may bypass the basal ganglia–thalamocortical abnormality and directly drive brainstem locomotor centers.

Keywords: Functional neuroimaging; Locomotor control; Basal ganglia; Gait disturbance; Parkinson's disease; Paradoxical movement

1. Introduction

Patients with Parkinson's disease (PD) often present with difficulty in initiating and/or maintaining walking, one of the basic symptoms that may start at anytime during the course of this disease. Furthermore, a problem with recovering from postural perturbation is also a disabling symptom. Gait disturbance in PD may respond to standard anti-Parkinsonian medication such as levodopa or dopamine agonists. Deep brain stimulation to the subthalamic nucleus or the globus pallidus may also be effective. These therapeutic effects suggest that gait disturbance in PD, at least in part, results from nigrostriatal dopamine deficiency and subsequent abnormality in the basal ganglia circuits. However, "on"-period freezing phenomena and postural symptoms in advanced cases are often refractory to these treatment options and profoundly hinder patients' quality of life. The pathophysiology of such "higher-level" gait disorders observed in PD and other conditions remains poorly understood [1], and further fundamental issues exist. Surprisingly, the question of which parts of the brain represent the control centers for human bipedal gait or station remains unknown. It would be fair to say that neural mechanisms of gait and posture controls remain the least understood among those of the human motor control system.

Insufficient knowledge of human gait mechanisms can largely be attributed to technical difficulty. Until recently, there had been no animal model of bipedal gait [2]. For motor or cognitive behavior other than gait, patients with organic lesions often provide invaluable insights into the underlying control mechanisms. However, organic lesions causing higher-level gait disorders are typically multiple or diffuse. Until now lesion studies have not provided specific information on the human "locomotor centers", except for rare case reports indicating the role of the dorsal brainstem. Recording physiologic signals such as electroencephalograms during walking is very challenging due to movement artifacts. With great efforts, it is possible to measure brain electric activity prior to gait initiation [3,4]. Neuroimaging, which has recently emerged as an

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important tool for brain mapping demonstrates similar methodological problems. In the last decade, however, several imaging techniques were developed specifically for the application to gait. These techniques have begun to cast light on the pathophysiology of gait disorders including PD. Herein, gait studies using neuroimaging methods in healthy subjects and gait disordered patients are reviewed with special emphasis on studies exploring the pathophysiology underlying Parkinsonian gait.

2. Neuroimaging methods available for studies of gait and station

Positron emission tomography (PET) with ^{15}O-labelled water, and more recently, functional magnetic resonance imaging have remained the mainstream of functional neuroimaging. Currently, however, it is almost impossible to investigate brain activity during actual gait using these methods. These scanning methods measure short-lasting signals related to regional cerebral blood flow (rCBF) or blood oxygenation changes following neuronal activity. Therefore, subjects are required to keep their head still while being scanned and, simultaneously, performing behavioral tasks. An exception to this is where brain activity during standing is measured using a particular PET scanner equipped with a mobile gantry [5]. Otherwise, researchers have studied brain activity during imaginary walking [6,7] or during lower limb movement [8] to investigate implications of gait control mechanisms.

Glucose metabolism during actual walking was successfully measured in an imaging experiment using PET with ^{18}F-fluorodeoxyglucose (FDG) [9]. One difficulty with the ^{18}F-FDG PET method is that subjects are required to walk for approximately 30 min, to allow for stabilization of the glucose metabolism measurement. Gait-disordered elderly patients may find it difficult to complete the task requirement.

Single photon emission computed tomography (SPECT) combined with ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) or ^{99m}Tc-ethylcysteine dimer (ECD) was found useful for the study of gait, despite poor spatial resolution compared with PET. The SPECT tracers are rapidly distributed to the brain in proportion to rCBF, are trapped there in a hydrophilic form, and remain stable for many hours [10]. In addition, the half-life of these technetium tracers is relatively long (~6 h). Therefore, it is possible to administer tracers while subjects are walking freely on a corridor or treadmill. Within a task period of ~5 min, tracers are fixed in the brain in proportion to rCBF. Several minutes following task completion, gait-induced rCBF information imprinted onto the brain is retrieved by scanning subjects immobilized on a scanner bed. The resultant brain images are often compared to ''snapshots'' of rCBF during task performance. This method allows the possibilty to measure gait-induced rCBF in the whole brain, including the cerebellum and basal ganglia. The number of repeated investigations in each individual is basically limited to two occasions: one for a task condition and the other for a control condition. These measurements can be performed sequentially, by splitting a regular dose of radiotracer into two (split-dose method). Using this split-dose SPECT method, brain activity during walking in healthy subjects and in patients with PD has been investigated [11–13].

More recently, Miyai et al. [14] have developed a system using near-infrared spectroscopy (NIRS) to investigate blood oxygenation changes on-line during gait. Since this method does not require a radiotracer injection and is completely non-invasive, it is possible to examine the same individual repeatedly with flexible task designs. Therefore, NIRS is particularly suitable for longitudinal follow-up of gait-disordered patients. Disadvantages with this method include low spatial resolution and inaccessibility to deep brain structures. The characteristics of each neuroimaging method are summarized in Table 1.

3. Neural structures subserving human bipedal gait and station: neuroimaging evidence

Voluntary movement usually consists of both automatic, hard-wired processes and willed processes. In the case of gait and station, basic control mechanisms appear inherently prepared for rhythmic alternation of lower limb movement, generation of adequate muscle tone, a postural reflex. These processes are executed mostly unconsciously, and subcortical structures such as the basal ganglia, brainstem, and spinal cord are

Table 1
Advantages and disadvantages of neuroimaging methods for gait study

	Application to gait	Spatial resolution	Whole brain coverage	Task duration	Individual assessment
FMRI/^{15}O–H_2O PET[a]	Limited	5 mm/5–10 mm	Possible	Flexible/~1 min	Possible
^{18}F-FDG PET[a]	Yes	5–10 mm	Possible	~30 min	Difficult
^{99m}Tc-PAO/ECD SPECT[a]	Yes	10–20 mm	Possible	~5 min	Difficult
NIRS	Yes	20–30 mm	Impossible	Flexible	Possible

[a]Methods involving radiation exposure.