Imaging: What Can it Tell Us About Parkinsonian Gait?

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ABSTRACT: Functional neuroimaging has provided new tools to study cerebral gait control in Parkinson's disease (PD). First, imaging of blood flow functions has identified a supraspinal locomotor network that includes the (frontal) cortex, basal ganglia, brainstem tegmentum, and cerebellum. These studies also emphasize the cognitive and attentional dependency of gait in PD. Furthermore, gait in PD and related syndromes like progressive supranuclear palsy may be associated with dysfunction of the indirect, modulatory prefrontal–subthalamic–pedunculopontine loop of locomotor control. The direct, stereotyped locomotor loop from the primary motor cortex to the spinal cord with rhythmic cerebellar input appears to be preserved and may contribute to the unflexible gait pattern in parkinsonian gait. Second, neurotransmitter and proteinopathy imaging studies are beginning to unravel novel mechanisms of parkinsonian gait and postural disturbances. Dopamine displacement imaging studies have shown evidence for a mesofrontal dopaminergic shift from a depleted striatum in parkinsonian gait. This may place additional burden on other brain systems mediating attention functions to perform previously automatic motor tasks. For example, our preliminary cholinergic imaging studies suggest significant slowing of gait speed when additional forebrain cholinergic denervation occurs in PD. Cholinergic denervation of the pedunculopontine nucleus and its thalamic projections have been associated with falls and impaired postural control. Deposition of β-amyloid may represent another non-dopaminergic correlate of gait disturbance in PD. These findings illustrate the emergence of dopamine non-responsive gait problems to reflect the transition from a predominantly hypodopaminergic disorder to a multisystem neurodegenerative disorder involving non-dopaminergic locomotor network structures and pathologies. © 2013 International Parkinson and Movement Disorder Society

Key Words: acetylcholine; amyloid; cerebellum; dopamine; gait; MRI; network; SPECT; Parkinson’s disease; pedunculopontine nucleus; PET; progressive supranuclear palsy

Gait and postural dysfunction presents early in Parkinson’s disease (PD),1 is a significant cause of disability, and responds poorly to dopaminergic replacement except in the early phase of the disease.2 Clinical characteristics of parkinsonian locomotor patterns include a slow and small-stepped gait with reduced angular excursion of the joints (eg shoulder, knee and trunk joints).3,4 PD affects “complex” gait activities, such as gait initiation, braking, and turning, which need modulation of the stereotyped (spinal) gait pattern. Akinesia, defined as inability to initiate movement or sustain movement (eg “sudden freezes”), is considered by some to be the fifth cardinal feature of PD.5 Freezing of gait (FOG), usually manifested as abrupt cessation of leg movement during walking, is a common cause of falls. Sudden freezes may be related to altered cortical regulation of movement execution together with progressive impairment of mesencephalic locomotor center function.6 The levodopa resistance of parkinsonian gait disturbances has been proposed to result from the extension of the degenerative process to non-dopaminergic structures.7 Here, we review first imaging studies of locomotor network functions in PD followed by neurochemical imaging studies that may underlie such network changes. We also discuss...
TABLE 1. Desired characteristics of imaging modalities used to study mobility

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>fMRI</th>
<th>rCBF SPECT &amp; FDG PET</th>
<th>([^{15}O]H_2O) PET</th>
<th>Neurotransmitter PET or SPECT</th>
<th>fNIRS</th>
<th>MEG/EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial resolution</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Temporal resolution</td>
<td>+++</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Subcortical definition</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>(EEG)</td>
</tr>
<tr>
<td>Actual gait</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>(EEG)</td>
</tr>
<tr>
<td>Portable</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>(EEG)</td>
</tr>
<tr>
<td>Non-radioactive</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</table>

fMRI, functional magnetic resonance imaging; rCBF, regional cerebral blood flow; SPECT, single photon emission computed tomography; FDG PET, \([^{18}F]\)fluorodeoxyglucose positron emission tomography; \([^{15}O]H_2O\), oxygen-15–labeled water; fNIRS, functional near infrared spectroscopy; MEG, magnetoencephalography; EEG, electroencephalography.

directions for future neuroimaging research to better understand mechanisms of parkinsonian gait disturbances. Specifically, we emphasize the need for future research based on correlation of imaging studies with improved and quantitative gait analysis assessments.

Imaging Methods and Human Mobility Functions

Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are molecular imaging techniques that use radiolabeled molecules to image molecular interactions of biological processes in vivo, such as binding of neurotransmitters, metabolism by cerebral enzymes, or regional cerebral blood flow (rCBF). The first in vivo human imaging studies of locomotion were performed using a radiotracer rCBF SPECT technique. Similar to rCBF oxygen-15–labeled water (\([^{15}O]H_2O\)) PET or regional cerebral glucose metabolic \([^{18}F]\)fluorodeoxyglucose (FDG) PET, these techniques suffer from poor temporal resolution and radiation exposure. The desired characteristics of a neuroimaging technique to study mobility include: high spatial resolution, high temporal resolution, whole brain (cortex/subcortical structures) imaging, imaging of actual gait or mobility functions, noninvasive, portable, cheap, no side effects, and compatible with implanted neurostimulators (Table 1).

However, currently, there is no imaging modality technique that meets all of these preferred criteria. With the exception of functional near infrared spectroscopy (fNIRS) and electroencephalography (EEG), SPECT, PET, magnetic resonance imaging (MRI), and magnetoencephalography (MEG) cameras are not portable. The use of functional MRI (fMRI) has allowed unique insights into brain network changes underlying mobility. Currently, fMRI is the only method that allows the investigation of whole brain activity and different gait conditions (eg gait initiation, turning, obstacle avoidance) in the same experiment. However, fMRI requires that the patient does not move the head during data acquisition. To overcome this problem, different paradigms have been developed to record cerebral blood oxygen level-dependent (BOLD) signals as an equivalent for brain activity during motor planning, during repetitive foot and leg movements, and during imagery of the motor function (motor imagery [MI]). The latter has been proven to be a very promising approach (for an in-depth review of this topic, see Maillet et al.\(^1\)). It is well known that neuronal networks show a substantial overlap between execution and imagery of a task. That is also a reason why MI is broadly used for training motor skills in sports and for relearning motor skills during rehabilitation. Miyai et al. compared treadmill walking (fNIRS) and MI (fMRI) and observed overlapping activity in the medial primary motor cortex (M1) and the supplementary motor area.\(^1\) Recently, it was observed that the locomotor network was very similar between actual walking (FDG-PET) and MI (fMRI).\(^1\) Furthermore, the network is specifically activated during imagery of active walking, but not during imagery of passive transfer or observing a second person’s walking.\(^1\) Based on these and other findings, MI is increasingly used to study human locomotion.

Imaging and Mobility: Network Correlates

The spinal pattern generators that provide the basic stepping pattern interact with sensory feedback and supraspinal structures to ensure flexible mobility. In analogy to cat electrophysiology and supported by human imaging data (Fig. 1), one can assume that prefrontal cortical areas are important for gait initiation and convey the locomotor signals through basal ganglia to brainstem locomotor regions.\(^1\) The subthalamic locomotor region (SLR) in the lateral hypothalamic area and the mesencephalic locomotor region (MLR), corresponding to the cuneiform and pedunculopontine nuclei in the dorsal midbrain, are disinhibited from tonic basal ganglia control for gait initiation.\(^1\) The cerebellar locomotor region (CLR), located close to the fastigial nuclei in the cerebellar midline, receives rhythmic input from the vermis and paravermal cerebellar cortex to control gait speed and variability.\(^1\) The CLR output converges with descending MLR projections in the pontine brainstem, where...
locomotor signals are transmitted to the spinal cord.

Imaging Studies on Parkinsonian Gait

Using rCBF SPECT and treadmill walking, PD patients exhibited less activity in the left medial frontal lobe, the right precuneus, and the left cerebellar hemisphere; whereas activity in the cerebellar midline, the right insula, and the left temporal and cingulated gyri was increased compared with controls. It is plausible that the increased activity in the insula may reflect increased sensory control, and the increased flow in cerebellar midline may compensate for frontal deficits in parkinsonian gait. FDG-PET at rest recently was used to assess the effect of a gait rehabilitation program in PD. Before therapy, patients showed hypometabolism in the right parietal lobe, the temporal lobes, and the left frontal lobe. Hypermetabolism was detected in the left cerebellum. After therapy, metabolism increased in the right cerebellum, the right parietal lobes, and the temporal lobes, showing an effect of the therapy both on physical performance and on supraspinal locomotor control.

Imaging Studies of Freezing of Gait

FOG is an extremely debilitating symptom of parkinsonian disorders with an unknown pathophysiological mechanism. Several studies have tried to localize...
the altered cerebral activity associated with FOG (for an overview, see Table 2; for a review, see Bartels and Leenders). These findings emphasize the disruption of cortical (particularly orbitofrontal and parietal) functions in patients with FOG, who also tend to have more severe caudate nucleus dopaminergic denervation. The involvement of typical nonmotor cortical areas may emphasize the cognitive and attentional dependency of gait in PD. However, a pitfall of these studies is that confounding effects of comorbid cognitive and mood changes in patients with FOG cannot be excluded.

A recent resting-state fMRI brain connectivity study identified reduced connectivity in the right cortical frontoparietal “executive-attention” and the right occipitotemporal “visual” networks in patients with FOG, who also tend to have more severe caudate nucleus dopaminergic denervation. The involvement of typical nonmotor cortical areas may emphasize the cognitive and attentional dependency of gait in PD. However, a pitfall of these studies is that confounding effects of comorbid cognitive and mood changes in patients with FOG cannot be excluded.

Deep Brain Stimulation (DBS) has become a routine treatment modality for patients with advanced PD. The effects of subthalamic nucleus (STN) DBS on gait and balance vary in PD, and the underlying mechanisms remain unclear. Hill and colleagues compared the effects of dorsal versus ventral STN regions on gait functions in PD using $^{15}$O$\text{H}_2$O PET in a within-subject design. These authors observed differential correlations with gait velocity and premotor cortex activity. DBS changes using ventral STN DBS, whereas dorsal STN DBS produced similar changes in the anterior cerebellum. Their findings suggest that the effects of STN DBS on gait may be mediated by different circuits, depending on the site of STN region stimulation through basal ganglia-thalamocortical circuits versus cerebellar-thalamocortical circuits. The findings also illustrate the complementary roles of basal ganglia and cerebellum in motor control.

Evidence that degeneration of the pedunculopontine nucleus (PPN) occurs in PD and the important role of the PPN in gait and postural stability, coupled with the finding that stimulation of the PPN in animal
models increases locomotor activity,\textsuperscript{35–37} led to interest in PPN stimulation for gait and postural dysfunction in PD.\textsuperscript{38,39} A \textsuperscript{15}O\textsubscript{H}2O PET activation study revealed that PPN DBS was associated with rCBF increases in the thalamus, cerebellum, midbrain region, and cortical areas involved in balance and motor control.\textsuperscript{40}

### Neurotransmitter Imaging Studies and Gait and Postural Functions in PD

The basal ganglia and the neurotransmitter dopamine have been key targets for research exploring the pathophysiology underlying movement disorders. The extent of nigrostriatal dopaminergic denervation can be quantified in PD using PET or SPECT techniques using DOPA decarboxylase, dopamine transporter (DAT), and vesicular monoamine transporter ligands. Such studies have demonstrated that striatal dopamine deficiency is most closely correlated with bradykinesia.\textsuperscript{41} Ouchi and colleagues reported on changes in dopamine availability in the nigrostriatal and mesocortical dopaminergic systems by gait in PD.\textsuperscript{42} Those investigators used DAT PET imaging before and after 1 hour of strenuous walking in patients with PD and a control group and observed that uptake in the striatum (specifically, the putamen) was decreased by gait to a greater extent in normal controls, whereas a significant reduction in DAT uptake was no longer present in the already denervated putamen but occurred in the caudate nucleus and orbitofrontal cortex in patients with PD. This shifted activity to predominant nonmotor structures of the anterior striatum and the mesocortical dopaminergic system may represent a key element in the pathophysiology of parkinsonian gait.

Evidence is accumulating that degeneration of both major cholinergic projection systems—the brainstem PPN and the basal forebrain corticopetal complex—is a major contributor to PD gait and postural dysfunction.\textsuperscript{33,44} We have observed that PPN-thalamic cholinergic innervation was reduced more severely in PD fallers compared with nonfallers,\textsuperscript{44,45} as confirmed by postmortem findings.\textsuperscript{46} These results are consistent with PPN degeneration as a cause of impaired postural control in PD (Table 3). We have preliminary data indicating that forebrain cholinergic degeneration is associated with slower gait speed in patients with PD, likely reflecting the degradation of attentional capacities.\textsuperscript{47} Gait speed is not significantly slower than normal in patients who have PD with predominant nigrostriatal dopaminergic denervation. These data suggest that forebrain cholinergic denervation is a more robust marker of slowing of gait in PD than nigrostriatal denervation alone and may reflect failing cognitive processing abilities during ambulation.

### Proteinopathy Imaging and Gait Disturbances in PD: Amyloidopathy

The Sydney Multicenter Study of Parkinson’s Disease revealed that longer duration of disease is increasingly accompanied by postmortem evidence of comorbid Alzheimer pathology, especially after 5 years.\textsuperscript{48} This time span agrees with epidemiological studies indicating the increasing dopamine unresponsiveness of (axial) motor symptoms in PD.\textsuperscript{49} We recently reported on the relation between postural instability and gait difficulty (PIGD) feature severity and neocortical $\beta$-amyloid burden in patients with PD who were at risk for developing dementia using \textsuperscript{11}C-Pittsburgh compound B (PiB) PET.\textsuperscript{50} We observed that increased PIGD feature severity was significantly associated with increased neocortical $\beta$-amyloid burden after controlling for effects of possible confounding variables, such as the degree of striatal dopaminergic denervation, age, and the degree of cognitive capacity impairment. These results are further substantiated by our preliminary finding of an association between higher neocortical $\beta$-amyloid burden and cadence (steps per minute). In contrast, there was no association between cadence and the degree of striatal dopaminergic denervation. It is noteworthy that the

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**Table 3. Neurotransmitter imaging studies in PD patients with gait difficulties or history of falls**

<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>References</th>
<th>Patient populations</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>AChE $[^{11}C]$-PMP PET</td>
<td>Bohnen et al.\textsuperscript{44,45}</td>
<td>PD fallers vs nonfallers</td>
<td>Decreased cholinergic PPN-thalamic activity in PD fallers without difference in striatal dopamine loss</td>
</tr>
<tr>
<td>AChE $[^{11}C]$-PMP PET</td>
<td>Gilman et al.\textsuperscript{72}</td>
<td>PD and atypical parkinsonian syndromes</td>
<td>Greater severity of gait and balance difficulties correlated with more severe cholinergic losses in the brainstem and cerebellum</td>
</tr>
<tr>
<td>AChE $[^{11}C]$-PMP PET</td>
<td>Bohnen et al.\textsuperscript{47}</td>
<td>PD and controls</td>
<td>Gait speed is not significantly slower than normal in PD patients with predominant nigrostriatal dopaminergic denervation but significantly slower in the PD subgroup with forebrain cholinopathy</td>
</tr>
</tbody>
</table>

AChE, acetylcholinesterase; $[^{11}C]$-PMP PET, 1-(carbon-11)methylpiperidin-4-yl propionate positron emission tomography; PPN, pedunculopontine nucleus.
inability to control cadence is associated with FOG in PD. These findings suggest that even low levels of comorbid neocortical amyloidopathy may significantly exacerbate gait impairments in PD.

Discussion

Neuroimaging studies of network functions provide support for a proposed model in which a corticostriatal loop of motor control involves functions of volition, cognition, and attention. In contrast, a subcortical-brainstem system seems to be required for the automatic regulation and modulation of muscle tone and rhythmic limb movements. Studies of FOG in PD emphasize the disruption of cortical (particularly orbitofrontal and parietal) functions related to this complex gait disorder. Imaging studies also identify the PPN and its thalamic and cerebellar connections as key network changes important for rhythmic functions of gait and postural control.

Gait and balance impairments in PD probably result from an intricate interplay of multisystem degenerations and neurotransmitter deficiencies. The hypothesis of a progressive extension of the degenerative process to nondopaminergic structures controlling locomotion has been put forward; and deficiencies in other neurotransmission systems involving acetylcholine, serotonin, and norepinephrine also have been evoked. PET imaging studies have demonstrated novel evidence of an extra-striatal nondopaminergic mechanism underlying gait and postural disturbances in PD: cholinergic denervation and cortical β-amyloid deposition. Therefore, the emergence of dopamine nonresponsive gait and postural problems may reflect the transition from a predominantly hypodopaminergic disorder to a multisystem neurodegenerative disorder involving cholinergic and other neurotransmitter projections. It is conceivable that cortical amyloid pathology may exert a disruptive effect on intrinsic cortical functions of motor control or may disrupt important subcortical (basal ganglia, thalamic, and cerebellar) to cortical connections. Although serotonergic denervation can be prominent in PD, at least in the forebrain, as demonstrated by serotonin transporter [¹¹C]-labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)benzonitrile (DASB) PET imaging, there have been no published reports of a relation between gait and serotonergic imaging studies. However, it is interesting to note that greater serotonergic denervation has been associated with greater β-amyloid deposition in PD, particularly in the striatum.

Future Directions

Need for Improved Understanding of the Role of the Cerebellum in Parkinsonian Gait

The cerebellum receives massive real-time sensory input. Proprioceptive sensory information is used not only to regulate ongoing movements but also to maintain stable standing posture. The cerebellar locomotor region, which is thought to regulate speed and gives rhythmic impulses to the brainstem and spinal cord, remains a largely unexplored area of research in parkinsonian gait. Functional MRI studies have demonstrated dynamic changes in cerebellar thalamocortical motor circuitry with increased cerebellar recruitment during disease progression. This is in keeping with the volumetric MRI findings of cerebellar atrophy only in older PD patients. Studies in the monkey have shown that, along with the well established cerebellothalamic projection, there is also a projection from the deep cerebellar nuclei to the PPN (cerebello-retticular projection). The recent development of a novel vesicular acetylcholine transporter (VACHT) PET ligand, [¹⁸F]fluoroethoxybenzovesamicol (FEOBV), provides an unprecedented opportunity to quantify cholinergic terminals, particularly PPN projections to the cerebellum. Our early observation of dense cerebellar vermis VACHT expression in our preliminary PET studies (Fig. 2) implicates an important cholinergic modulation of cerebellar control of posture. The use of VACHT imaging may provide a novel tool for exploring cholinergic cerebellar functions of PD mobility changes.

Need for Improved Understanding of the Role of Noradrenergic Denervation in Parkinsonian Gait

Noradrenergic pathways have been implicated in alertness and other cortical attention functions important for gait control in PD. The locus coeruleus is a small nucleus located in the pontine tegmentum and is the main source of norepinephrine for the brain and spinal cord. There is significant degeneration of the locus coeruleus in PD. We have preliminary findings indicating that cardiac postganglionic sympathetic...
denervation correlates with gait velocity in PD independent from the degree of nigrostriatal denervation. However, it remains uncertain whether cardiac sympathetic denervation can be taken as a proxy for central noradrenergic degeneration in PD. Future research using novel ligands that allow direct quantitative assessment of central noradrenergic activity is needed.

Need to Correlate Imaging Findings With Neurophysiology of Gait

Advanced MRI techniques are providing optimal spatial resolution. Ultrahigh-field scanners (≥ 7.0 Telsa) and quantitative MRI techniques, including diffusion tensor MRI and susceptibility-weighted imaging, hold substantial promise for an accurate quantification of tissue injury in involved brain areas. Combined with sophisticated postprocessing, such as voxel-wise mapping and tractography, these techniques are contributing to the characterization of in vivo pathologic substrates of the clinical manifestations of PD. What is lacking so far is a good correlation of the imaging findings and parameters like gait variability, dual task ability, or frequency of falls based on quantitative gait and postural assessments. Studies that combine imaging and quantitative gait assessment will help to elucidate how the brain network interacts with gait and postural control.

Need to Correlate Selective Stimulation Protocols in Deep Brain Stimulation to More Accurately Predict Connectivity Patterns and Interaction of Specific Centers in the Supraspinal Locomotor Network of Parkinsonian Gait

Selective stimulation of implanted DBS targets combined with rCBF imaging can provide a unique experiment of nature to better characterize the connectivity patterns of the various locomotor centers underlying parkinsonian gait. For example, the recent study by Hill and colleagues provides early evidence that the effects of STN DBS on gait may be mediated by different circuits through basal ganglia-thalamocortical versus cerebellar-thalamocortical circuits. Recordings of local field potential from implanted electrodes can provide additional important physiological information about gait parameters at key locomotor areas, such as the PPN.

Need for Standardized Paradigms for Functional Imaging in PD

Emerging areas for future development include the development of new fMRI motor imagery paradigms, the use of portable devices (fNIRS, EEG), and the application of multimodal imaging (EEG-fMRI, PET-fMRI). However, it will be crucial to define standards for finding the best method for a given research question. fMRI remains the best method for depicting subcortical structures and for repetitive measurements. EEG has excellent temporal resolution and will make it possible to investigate changes in brain activity during the gait cycle. A recent study by Handojoseno et al. successfully demonstrated the feasibility of using novel ligands that allow direct quantitative analysis for the early detection of FOG in PD that may appear electrically 5 seconds before the clinical symptoms. FDG-PET is well suited for cognitively impaired patients, because it does not require the same amount of cooperation as fMRI with MI of gait.

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References


