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PET studies in Parkinson's disease motor and cognitive dysfunction

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SUMMARY

Positron emission tomography (PET) has led to significant advances in the knowledge of the neurobiology and pathophysiology of Parkinson's disease (PD) and has also greatly contributed to the understanding of potential mechanisms involved in the development of treatment-induced complications. Initially, PET was mostly used to assess *in vivo* the severity of the nigrostriatal dopaminergic dysfunction and the resulting motor symptomatology in PD. It has been demonstrated that PET measurements of putaminal dopaminergic function, as measured by [^{18}F]-Fluorodopa uptake, correlate well with stages of disease and symptom severity in PD patients, particularly with bradykinesia and rigidity.

Analysis of metabolic changes across the brain has identified specific brain networks associated with the main motor features of the disease, including bradykinesia and tremor.

In more recent years, the growing availability of new imaging radiotracers for monoaminergic and cholinergic neurons has enabled the evaluation of the non-dopaminergic brain pathways that are likely to be involved in the pathophysiology of non motor symptoms of PD, including depression, fatigue, sleep disorders, and cognitive impairment. Finally, β-amyloid imaging agents have been used to assess the influence of coexistent cortical Alzheimer pathology in PD. This review summarizes the findings from PET studies that have investigated pathophysiology and treatment of motor dysfunction and cognitive impairment in PD.

1. Introduction

Parkinson's disease (PD) is a chronic and progressive degenerative neurological disorder characterized by the formation of proteinaceous intraneuronal inclusions, which are referred to as Lewy bodies and Lewy neurites, and the degeneration of dopamine neurons in the substantia nigra par compacta. The degeneration of the dopaminergic nigrostrial pathway alters the normal functioning of the basal ganglia–thalamo-cortical circuits and is responsible for the occurrence of the classical motor symptoms of PD, including poverty of movement, increased muscle rigidity, and tremor. However, the pathological process in PD is not confined to the dopaminergic system, as initially thought. Serotoninergic, cholinergic, and noradrenergic pathways, along with several other central neurotransmitter and neuromodulator systems have been found to be abnormal in the brains of patients with PD. Dysfunction of the non-dopaminergic systems seems to play a role in the development of non-motor symptoms such as fatigue, depression, sleep disorders, and cognitive impairment.

Positron emission tomography (PET), along with other *in vivo* functional neuroimaging techniques have hugely contributed to our knowledge of the neurobiology and pathology of PD and the pathophysiological mechanisms underlying the complex symptomatology of the disease. This review focuses on the findings of PET studies that examined the neuronal correlates of motor dysfunction and cognitive impairment in patients with PD.

2. Imaging motor dysfunction in PD

In vivo visualization of the nigrostriatal dopaminergic pathway is one of the most fundamental uses of PET and other functional neuroimaging techniques in PD research. PET has shown high sensitivity and specificity for detecting striatal dopamine deficiency in PD patients, which can be quantified by assessing dopamine synthesis and storage in the presynaptic terminals with [^{18}F]-Fluorodopa (Fig. 1), or by measuring availability of presynaptic dopamine transporter (DAT) or vesicular monoamine transporter 2 (VMAT2). In the striatum, both DAT and VMAT2 are expressed in dopaminergic terminals and can therefore be used as specific markers of integrity of nigrostriatal projections. Currently, several PET radioligands can be used for DAT imaging, whereas [^{11}C]-dihydrotetrabenazine (DTBZ) is the only ligand available for VMAT2.

The relationship between striatal dopaminergic deficiency and severity of motor symptoms is well established. A significant inverse correlation has been found between Hoehn and Yahr score and

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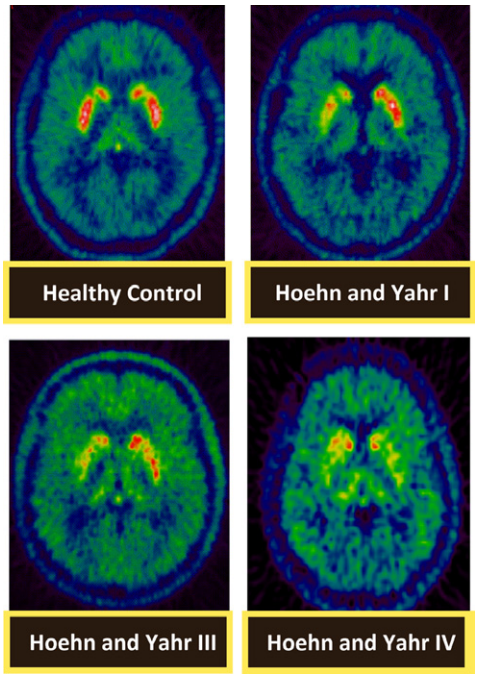

Fig. 1. Images of striatal [^{18}F]-Fluorodopa uptake in a healthy control and three PD patients at various Hoehn & Yahr stages.

[^{18}F]-Fluorodopa uptake in both putamen and caudate nucleus [1]. Additionally, putaminal [^{18}F]-Fluorodopa uptake correlates well with total UPDRS motor score [1] and with specific clinical features, especially with bradykinesia and rigidity [2]. Finally, a significant negative correlation has also been found between total motor UPDRS score and uptake of the PET DAT ligand [^{18}F]-FP-CIT in caudate nucleus, anterior putamen and posterior putamen [3].

[^{18}F]-fluorodeoxyglucose (FDG) PET measures regional cerebral glucose metabolism. Analysis of metabolic changes across the brain has identified specific brain networks associated with bradykinesia and tremor. The Parkinson's disease-related profile (PDRP), which correlates well with measures of bradykinesia, comprises a relative hypermetabolism of the lentiform nucleus, thalamus, and pons, covarying with a relative hypometabolism of the lateral frontal cortex [4].

Conversely, parkinsonian tremor seems to be mediated by a distinct metabolic network involving primarily cerebello-thalamo-cortical pathways, so-called PD tremor-related metabolic pattern (PDTP) [5].

The involvement of serotonergic system in the pathogenesis of motor symptoms in PD has been assessed with [^{11}C]-WAY 100635, a PET ligand for the serotonin 5-HT$_{1A}$ receptor [6]. Compared with healthy volunteers, PD patients showed a mean 27% reduction in [^{11}C]-WAY 100635 binding in the midbrain raphe, which is likely to reflect reduced serotonin 5-HT$_{1A}$ receptor availability. Individual reductions in raphe [^{11}C]-WAY 100635 binding correlated well with composite tremor scores, but not with rigidity or bradykinesia, suggesting that serotonin may be involved in the etiology of rest tremor in PD.

Many patients with advanced PD develop gait and balance problems which can lead to recurrent falls and are not improved by dopaminergic therapy.

Bohnen and colleagues [7] used PET with the acetylcholine analogue [^{11}C]-PMP to investigate acetylcholinesterase (AchE) activity in 17 PD patients with a previous history of recurrent falls and 27 patients who had no falls. Each patient also had [^{11}C]-DTBZ PET to measure nigrostriatal dopaminergic function. While nigrostriatal dopaminergic activity was similar between fallers and non-fallers, the former had significantly lower thalamic AchE activity than both controls and PD non-fallers. Such a loss of thalamic cholinergic function is likely to reflect dysfunction/degeneration of the pedunculopontine nucleus, which is the principal source of cholinergic innervation to the thalamus. These findings therefore suggest an association between cholinergic dysfunction and tendency to fall in PD and indicate a possible new therapeutic strategy for the treatment of this symptom.

The relationship between clinical improvement and striatal dopamine release induced by levodopa administration in advanced PD has been investigated with [^{11}C]-raclopride PET [8]. Improvements in UPDRS scores induced by levodopa were significantly correlated with reductions in putaminal [^{11}C]-raclopride, which are indicative of dopamine release. Improvements in rigidity and bradykinesia were also correlated with putaminal dopamine release, but this was not the case for tremor or axial symptoms, confirming that non-dopaminergic and/or extra-striatal mechanisms may underlie these symptoms.

Another important finding of this study is that large putaminal [^{11}C]-raclopride binding changes were correlated with higher dyskinesias scores, indicating that the occurrence of dyskinesias after a single dose of oral levodopa is associated to the level of dopamine generated in the synaptic cleft. However, it is likely that dyskinesias in PD arise due to a combination of several presynaptic and postsynaptic mechanisms within the basal ganglia network.

3. Imaging cognitive dysfunction in PD

Cognitive impairment is common in PD. Compared to the general population of the same sex and age, PD patients have a six-fold higher risk of developing dementia and approximately 75% of patients who survive for more than 10 years develop dementia. Additionally, a range of cognitive dysfunctions including impairment of visuospatial capacities, attentional control, and working memory have been reported also in non-demented PD patients and may occur even in the early stages of the disease.

The pathophysiology of cognitive dysfunction in PD is heterogeneous.

Several PET studies have suggested that many of the cognitive deficits in moderate stage PD may be caused by the striatal dopaminergic depletion and associated dysfunction of frontostriatal pathways. A statistically significant positive correlation has been found between reduced [^{18}F]-Fluorodopa uptake in the caudate nucleus and poor performance on tests of visual memory and immediate and delayed verbal memory [9]. In another study, decreases in the putaminal [^{18}F]-Fluorodopa uptake predicted performance on the Wisconsin Card Sorting Test in fifteen non-demented PD patients [10]. Finally, network analysis of metabolic changes across the brain has shown that the networks subserving executive dysfunction (assessing strategy and planning, and working memory) in PD patients are characterized by relative ventromedial frontal, hippocampal, and striatal hypometabolism, associated with mediodorsal thalamic hypermetabolism. Interestingly, this pattern is different from that associated with bradykinesias, suggesting that these two clinical abnormalities reflect different aspects of subcortico-cortical dysfunction [11].

In patients with more advanced disease, the degeneration of the medial substantia nigra and ventral tegmentum and the subsequent loss of mesolimbic and mesocortical dopaminergic projections may also contribute to the development of dementia. Indeed, voxel-by-voxel comparison of [^{18}F]-Fluorodopa parametric images of PD patients with and without dementia has shown that the formers have additional [^{18}F]-Fluorodopa uptake reductions in the right caudate and bilaterally in the ventral striatum and the anterior cingulate [12].

PET studies of brain metabolism with FDG have shown decreased resting metabolic activity in various cortical regions in both