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The application of network mapping in differential diagnosis of parkinsonian disorders

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Abstract

Although approximately 1–3% of the population over age 65 have Parkinson's disease (PD), only about 75% of the patients diagnosed with parkinsonism have PD. The differential diagnosis of parkinsonian disorders based on clinical symptoms alone is particularly difficult during the early stages of the disease. A number of imaging strategies have been developed to differentiate between these clinically similar conditions. The assessment of abnormal patterns of brain metabolism, either by visual inspection or using computer-assisted algorithms, can be used to discriminate between classical PD and atypical variant conditions such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), or corticobasal ganglionic degeneration (CBGD).

Recent advances in network quantification routines have created the basis for fully automated differential diagnosis. Using PET, investigators have identified specific disease-related spatial covariance patterns that are characteristic of PD and its variants. By computing pattern expression in individual patient scans, it has become possible to determine the likelihood of a specific diagnosis. In this review, we describe the various imaging techniques that have been used to diagnose PD with emphasis on the application of network tools. Analogous methods may have value in the assessment of other neurodegenerative and neuropsychiatric conditions.

Keywords: Parkinsonism; Positron emission tomography; Brain metabolism; Differential diagnosis; Network analysis; Spatial covariance patterns

1. Introduction

Idiopathic Parkinson's disease (PD) is a relatively common disorder with a prevalence of 1–3% in the population over 65 years of age [1]. Clinically, parkinsonism is characterized by the existence of at least two of the following motor symptoms: tremor, hypokinesia, and rigidity. Classical PD is differentiated from other parkinsonian disorders such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal ganglionic degeneration (CBGD), and Lewy body dementia (DLB) by a combination of an asymmetry of symptoms, possible presence of a resting tremor, and a long-term responsiveness to levodopa.

The differential diagnosis of parkinsonian disorders based solely on clinical symptoms remains unsatisfactory in that only 76% of patients thought to have PD prove to have this diagnosis at postmortem [2]. The overall assessment of a trained movement disorder specialist after clinical follow-up has been shown to provide the most accurate diagnosis [3]. However, differentiation of these disorders by clinical assessment alone can be difficult in the earliest stages of disease. Indeed, the clinical diagnosis made by a movement disorder specialist at the initial visit had to be changed in approximately one-third of patients by the fifth year of symptoms [3].

Early differential diagnosis in patients with parkinsonism is important for prognosis and the course of treatment. While the life expectancy of PD patients resembles that of

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their healthy contemporaries, that of patients with atypical parkinsonian syndromes such as MSA, PSP, and CBGD, is markedly reduced. Moreover, patients with atypical parkinsonian syndromes generally do not benefit from pharmacologic and surgical interventions, although they can potentially experience the side effects of these therapies [4]. Accurate differential diagnosis of parkinsonian syndromes at the earliest stages of disease is also important for the optimal assessment of disease modifying agents. Newly diagnosed, *de novo* PD patients are often enrolled in these treatment trials. However, specific signs differentiating PD and parkinsonian syndromes (e.g., responsiveness to dopaminergic therapy) are often not well articulated at early clinical stages of disease. The enrollment of such patients might result in inaccurate study results. Considering the importance of early differential diagnosis, it is not surprising that a number of neuroimaging techniques have been developed to improve the accuracy of discriminating between PD and its clinical look-alikes.

Widely available neuroimaging modalities such as position emission tomography (PET) and single photon emission computed tomography (SPECT) have provided novel insights into the pathophysiology of PD and other parkinsonian syndromes [5]. In PD, radiotracer-based imaging studies have been applied to assess nigrostriatal presynaptic function. Functional imaging techniques have also been used to study neuronal activity by quantifying regional glucose metabolism and cerebral blood flow in the resting condition. These assessments have contributed considerably to the understanding of abnormal neuronal circuitry underlying the pathophysiology of parkinsonism [6]. Other imaging methods used for differential diagnosis include cardiac sympathetic denervation and various magnetic resonance imaging (MRI) techniques.

In this review, we will discuss the relative advantages and shortcomings of radiotracer-based imaging techniques in the clinical diagnosis and management of PD as well as the potential use of network mapping techniques to differentiate between PD and its atypical variants.

2. Imaging dopaminergic function in parkinsonism

Neurodegenerative diseases, particularly those affecting the basal ganglia and related pathways, are often associated with the loss of nigrostriatal dopaminergic projections. The integrity of this system can be assessed by neuroimaging methods utilizing radioligands that bind to pre- or postsynaptic components. On the other hand, the functional status of the basal ganglia efferent projections can be assessed using imaging to assess regional cerebral blood flow and metabolism as measures of neural activity.

2.1. Presynaptic dopaminergic imaging

The most commonly applied PET radiotracer to assess the integrity of presynaptic nigrostriatal dopaminergic nerve terminals is [^{18}F]fluorodopa (FDOPA) (see [7]). PET studies with this tracer measure the rate of decarboxylation of [^{18}F]fluorodopa to [^{18}F]fluorodopamine by dopa decarboxylase (DDC) and its subsequent storage in the striatal dopaminergic nerve terminals.

FDOPA PET scans have routinely been analyzed by a multiple time graphical approach incorporating plasma or brain input functions [8], or by formal compartmental models to estimate the specific rate constant for striatal DDC [9,10]. Subsequent studies revealed that the striato-occipital ratio (SOR) for FDOPA determined from a single 10-min 3D PET scan can be as accurate as the more complex measures [8,11,12]. FDOPA PET measurements have been used to obtain objective correlates of disease severity and to discriminate early stage PD patients from patients with essential tremor, psychogenic movement disorders, and healthy control subjects (for review see [5]).

FDOPA PET has also been used to differentiate among parkinsonian syndromes [13]. In patients with early stage PD, FDOPA uptake is relatively preserved in the caudate and anterior putamen. By contrast, in patients with atypical parkinsonian syndromes such as MSA, equivalent impairment of FDOPA uptake can be observed in the caudate and the putamen [14]. However, these dopaminergic signatures are often insufficient to discriminate PD from atypical parkinsonism at early clinical stages [15]. Indeed, striatal FDOPA uptake can be reduced in other parkinsonian movement disorders such as MSA, PSP, Wilson's disease [16], Guamanian amyotrophic lateral sclerosis (ALS–PD complex; [17]), and X-linked Filippino dystonia parkinsonism [18]. Additionally, asymmetrical parkinsonian syndromes such as HPHA and CBGD can show relative reductions in basal ganglia FDOPA uptake contralateral to the affected side [19,20].

2.1.1. DAT binding

The development of radiotracers that bind to the striatal dopamine transporter (DAT) has led to another means for directly imaging the nigrostriatal dopaminergic system with PET or SPECT. DAT enables the release and reabsorption of dopamine in the nigrostriatal intersynaptic cleft. A number of radiotracers, mostly cocaine analogs, have been developed to quantify striatal DAT binding as an objective marker of the integrity of presynaptic nigrostriatal dopamine terminals (see [7], for review). The most extensively studied agents in this category are the cocaine analogues, such as 2-β-carbomethyl-3β-(4-iodophenyl) tropane (βCIT) and its fluoroalkyl esters [21]. Striatal DAT binding can be quantified by any of these agents, which differ primarily in the time of attained equilibrium and the duration of the scanning procedure.

The major application of DAT binding imaging procedures has been to assess the rate of decline in presynaptic dopaminergic function in PD patients. In SPECT studies using [^{123}I]βCIT [22], striatal DAT binding declined by 7.1% per year in short duration PD, and 14.9% in short duration atypical parkinsonian syndromes. The rate of decline in PD appears to slow markedly with evolving disease [22]. In