

Brain MRI in Parkinson's disease

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1. ABSTRACT

In this review article, conventional brain MRI and advanced MRI techniques in Parkinson's disease (PD) are discussed, with emphasis on clinical relevance. Conventional brain MRI sequences generally demonstrate limited abnormalities specific for PD and in clinical practice brain MRI is mainly used to exclude other pathology. Possibly, brain MRI at higher magnetic field strengths could provide new diagnostic markers. In recent years, new imaging techniques such as susceptibility weighted imaging (SWI), diffusion (tensor) MRI, magnetization transfer imaging (MTI), and functional MRI (f-MRI) have been applied to patient cohorts with PD to improve understanding of pathophysiologic changes, including functional connectivity. These advanced MRI techniques hold promise to provide additional diagnostic markers for early stage PD, as demonstrated by diffusional changes in the orbital-frontal region in the pre-motor phase of PD. Whether these advanced MRI techniques provide new diagnostic markers for early stage PD, remains a debate. Standardization of scanning protocols and post-processing methods, and validation of diagnostic criteria is crucial for these advanced MRI techniques. For this, well designed prospective clinical cohort studies are needed.

2. INTRODUCTION

Parkinson's disease (PD) is a late-onset neurodegenerative disorder with increased prevalence at raising age, and the most frequent cause of parkinsonism. PD is currently defined clinically by the presence of bradykinesia and at least one further motor symptom such as rest tremor or rigidity (1). Non-motor symptoms seem to be an integral part of the clinical spectrum of PD and some of these changes may predate the onset of motor symptoms (2). These include cognitive dysfunction, depression, hyposmia, as well as complex behavioral disorders.

The primary pathologic changes in PD involve loss of nigrostriatal dopaminergic neurons and intraneuronal Lewy bodies in the ventrolateral and caudal segment of the substantia nigra pars compacta (3,4). The substantia nigra consists of the pars compacta (SNpc), which serves mainly as an input to the basal ganglia circuit supplying the striatum with dopamine, and the pars reticulata (SNpr) which serves mainly as an output, conveying signals from the basal ganglia to numerous other brain areas. The SNpc contains subgroups of dopamine-containing neurons, so-called nigrosomes, of which nigrosome 1 is the largest (5). In post-mortem studies, it is

shown that dopaminergic loss in PD is higher in the nigrosomes than in other SN subregions, with maximal loss in nigrosome1 (6). In later disease stages, additional lesions arise in non-dopaminergic brain areas (7). The main anatomical and functional changes induced by PD can be divided into three different areas: mesencephalic (dopaminergic neural loss), basal ganglia (dopaminergic depletion) and cortical (functional reorganization) (8).

In clinical practice, differentiating Parkinson's disease from the various forms of neurodegenerative atypical parkinsonism (AP) can be difficult, especially in early disease stages. Neurodegenerative atypical parkinsonism includes separate disease entities such multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and cortical basal degeneration (CBD). There is a debate whether Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB) are the same disease entities (9). Misdiagnosis rates in patients presenting with parkinsonism as high as 24% have been reported (10,11). Adequate recognition of the proper diagnosis influences the counseling of patients, and to some extent also treatment. During clinical neurological examination, recognition of various atypical findings is important (also referred to as 'red flags') as these can be suggestive for AP (12). Examples of such red flags include subtle cerebellar ataxia, prominent or early autonomic dysfunction, inability to ride a bicycle, or fixed dystonia. As many signs become apparent in later disease stages, it is challenging to make the correct diagnosis in early disease stages. For this reason, there is a need for ancillary investigations to improve the diagnostic accuracy.

Brain MRI is commonly used in clinical practice to evaluate structural brain anatomy and pathology. In neurodegenerative pathology, brain MRI can identify patterns of structural degradation in order to help make the correct diagnosis. These structural changes can be regions of atrophy or structure signal intensity changes. In the diagnostic work-up of patients with parkinsonism, it is recommended to perform brain MRI (13). The main purpose of brain MRI in the work-up of parkinsonism is to assess cerebrovascular damage (vascular parkinsonism), and to exclude other possible but more rare causes of parkinsonism such as multiple sclerosis, normal pressure hydrocephalus or Wilson's disease. Also, it can support the diagnosis of neurodegenerative atypical parkinsonism.

Conventional brain MRI has limited added value for the differentiation between PD and AP when clinical certainty is already high, but has some added diagnostic value when the clinical diagnosis is still uncertain (14). Conventional brain MRI includes T1 weighted sequences to evaluate anatomical structures, T2 weighted sequences (including T2 fluid attenuated inversion recovery, FLAIR sequence) sensitive to tissue property changes, and proton density sequences which combines T1 and T2 sequence properties.

In recent years, new imaging techniques have been applied to patient cohorts with PD and AP to improve understanding of pathophysiologic changes, including functional connectivity. These new MRI techniques are

promising for clinical application in order to improve the differentiation between PD and AP in early disease stages. These advanced imaging techniques include susceptibility weighted imaging (SWI), diffusion (tensor) MRI, magnetization transfer imaging (MTI), and functional MRI (f-MRI). In this review article, conventional brain MRI and advanced MRI techniques in Parkinson's disease are discussed, with emphasis on clinical relevance.

3. BRAIN MRI IN PARKINSON'S DISEASE

3.1. Conventional imaging sequences

Routine brain MRI is usually normal in early PD, or will show age-related changes (15). Later on, cortical atrophy of the frontal or temporal lobe can be seen (16) as illustrated in Figure 1A. These regions of atrophy can be assessed quantitatively by measurements of diameters and areas or by voxel-based morphology (VBM) in which a 3D isotropic voxel T1 sequence is used (e.g. T1 MP-RAGE sequence). VBM enables operator-independent and automated detection of differences between groups. Using VBM, gray matter loss in cortical areas in the frontal lobe have been reported in PD (17). Cortical atrophy may be related to the development of dementia in PD, especially when the limbic/paralimbic, anterior cingulate and subcortical grey matter structures are involved (17-19). For routine clinical diagnostic work-up, the use of VBM is limited as no clear diagnostic criteria have been defined or validated.

On T2 weighted images, the SNpr corresponds to an area of low signal intensity and the SNpc to an area of relatively high signal intensity. In advanced disease stages, narrowing of the space between the substantia nigra pars compacta and the pars reticulata can sometimes be seen (20). Also, the SN can demonstrate signal increase on T2 sequences, and initial studies were promising for the T2 sequence to identify reduced width of the SNpc in PD (21). As it is difficult to demarcate the SN borders, especially the boundary between the SN and the crus cerebri, the use of conventional sequences to evaluate the SN to diagnose PD was not reliable. Inversion recovery (IR) imaging to suppress white and grey matter signal was proposed to better depict the SN in order to discriminate between PD and healthy controls (22,23) and first results were promising though the study population was small (24). More recent automated comparison with SN histograms proved better (25), however additional validation is necessary to evaluate its diagnostic value in clinical practice.

In their study, Blazejewska *et al.* demonstrated *in vivo*, and post-mortem with histological correlation, that high resolution 7T MRI can directly visualize nigrosome 1 (26). In all 10 PD cases, there was consistent bilateral absence of this nigrosome in PD, and present in 7/8 healthy control cases. The absence of nigrosome 1 in the SNpc on high resolution MRI might be a new diagnostic feature for PD. Their findings are in line with results published by another group (27).

Conventional brain MRI has high specificity for different forms AP, though sensitivity is low mainly in early

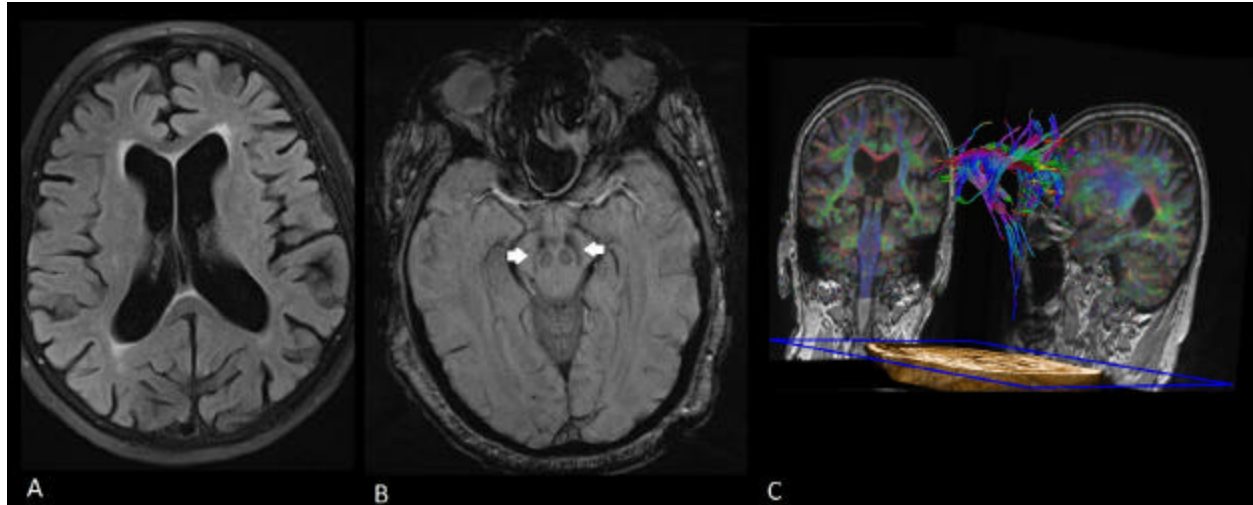


Figure 1. Patient diagnosed with Parkinson's disease. Conventional 3 Tesla brain MRI T2 FLAIR sequence (A) showing non-specific cortical atrophy with sulcal widening and enlargement of the lateral ventricles. Susceptibility weighted imaging (B) demonstrating mineralization of the reticulate part of the substantia nigra (arrows), and diffusion tensor imaging with tractography (C) for the evaluation of the corpus callosum.

disease stages (14,28). In the putaminal form of MSA, atrophy and T2 hypo-intense signal intensity changes of the putamen can be observed. In the cerebellar form of MSA, atrophy and cruciform T2 hyper-intense signal intensity changes of the pons ('hot cross bun' sign) as well as T2 hyper-intense signal intensity changes of middle cerebellar peduncle and cerebellar atrophy can be seen. In PSP, midbrain atrophy ('hummingbird' sign) and T2 hyper-intense signal intensity changes in the superior cerebellar peduncle can be observed. The hallmark of CBD is asymmetric cortical atrophy, mainly of the parietal lobe.

3.2. Advanced imaging sequences

3.2.1. Susceptibility weighted imaging

Magnetic susceptibility indicates the degree of magnetization of a material in response to an applied magnetic field. The induced magnetization is directly proportional to the main field and the magnetic susceptibility characteristics of the substance. Most diagnostic MRI sequences rely on the reading of magnitude information and the phase information is not used (29). SWI uses both magnitude and phase information to generate images as phase images contain information about local susceptibility changes between tissues. Each tissue behaves differently in a magnetic field and SWI can be useful in measuring iron content and other substances that change the local magnetic field (30,31) (Figure 1B). Using a standard T2 sequence as a measure of mineralization is unreliable, as it is also affected by factors such as myelin loss and changes in water concentration, which vary within tissue type, presence of disease, and age (31-33).

A number of neurodegenerative disorders are associated with increased iron levels in specific regions in the brain. In some diseases it is clear that disturbances of brain iron metabolism results in tissue damage because of oxidative stress, such as the group of genetic disorders in

Neurodegeneration with Brain Iron Accumulation (NBIA). Patients with NBIA can present with clinical symptoms of parkinsonism, but disease onset is typically at young age. Brain MRI with SWI can be of added value for diagnosis and differentiation between NBIA subtypes (34). In other diseases, such as Parkinson's disease, brain iron accumulation is seen in specific areas of the brain in which it is not clear whether this iron accumulation is a primary cause of the neurodegenerative process or a secondary response to neurodegeneration. Also, neurodegenerative pathologic susceptibility changes should be differentiated from normal aging brain changes (35).

There are conflicting reports with regard to changes of iron content in the SN in PD (36). In a study using SWI to study 40 patients with PD and 26 age- and sex-matched healthy controls, increased susceptibility in the SN in PD was found, which did not correlate with disease duration but did correlate with severity of motor symptoms (37). Increased susceptibility in the SN in PD in comparison to healthy controls has been reported in other studies using SWI as well (38,39), though Gupta *et al.* did not find susceptibility differences of the SN between PD and healthy controls (40).

When evaluating pathologic susceptibility changes in other brain structures in patients presenting with parkinsonism, these are mainly found in AP. Wang *et al.* found increased iron deposition in the entire putamen and pulvinar thalamus in patients with MSA-P, which enabled differentiation between MSA-P and PD (39). Gupta *et al.* found greater susceptibility of the putamen, red nucleus and substantia nigra in PSP which differentiated PSP from PD and MSA-P (40). No correlation between disease severity and degree of mineralization in any of the groups was seen.

Another more practical application of SWI is the improved identification of the subthalamic nucleus, which is

of value for targeting deep brain stimulation surgery in PD (41).

3.2.2. Diffusion MRI

Diffusion weighted imaging (DWI) quantifies the random movement of water molecules, expressed as mean diffusivity (MD). Restriction of the random motion of water molecules by the normal architecture of glial tissue and fiber tracts is called anisotropy. Fractional anisotropy (FA) used in diffusion tensor imaging (DTI) estimates the degree of anisotropy, either quantitatively or to perform tractography (Figure 1C). Changes in diffusivity seem to represent a quantitative measure of microstructural integrity of white matter tracts and grey matter structures, and accordingly microstructural damage in neurodegenerative disorders. The main methods to analyze quantitative diffusional data include the region-of-interest (ROI) method and voxel-based analyses (VBA), of which tract-based spatial statistics (TBSS) is commonly used to study white matter tracts.

Changes in FA values have been reported throughout the brain in premotor PD, even when no significant atrophy is seen (42). Reduced FA values in PD patients compared to healthy controls have been reported in the motor, premotor and supplementary motor cortex (43,44). In addition, decreased FA values and increased MD values in the genu corpus callosum have been reported in early stage PD, which could indicate degeneration of the interhemispheric axonal connections between frontal areas (45). This is supported by the finding of significantly decreased FA values without volume loss in the frontal lobes in PD patients compared with age-matched controls (46). These microstructural changes in the frontal lobe can be the result of pathologic changes outside the substantia nigra in PD, but may also reflect frontal lobe dysfunction which is common in early stage PD (47).

Inconsistent results have been published regarding diffusional changes in the SN in PD. Decrease of FA in the SN have been found in early disease stages of PD (48-50). Greater reduction of FA in the caudal region compared with the rostral region of the SN has been observed with complete discrimination between early untreated PD patients and healthy controls (51). This location seems to be in accordance with earlier described changes in the nigrosome1 region of the SNpc. Other studies did not find differences in SN diffusivity measures between PD patients and healthy controls (52,53). Also, there is debate whether a correlation exists between disease severity and FA in the SN. Some studies reported a correlation (44), whereas others did not (51,54).

Two recently published systematic reviews, differed in their conclusion whether SN diffusional changes can be used as a diagnostic marker (55,56). Cochrane *et al.* found highly significant PD induced FA reduction in the substantia nigra, but a much smaller variation in results comparing the different studies (55). Based on their DTI study on 59 subjects (32 PD patients and 27 matched healthy controls) together with a systematic review and meta-analysis of available published reports, Schwarz *et al.* conclude that there is insufficient evidence for nigral DTI

measures to serve as a useful diagnostic marker of PD at this point in time (56). Differences in studies included in these two meta-analyses as well as a variation of extracted values from included studies could explain their contradicting conclusions (56). Schwarz *et al.* stress the need for standardization of the anatomical position of SN/SNpc, especially for ROI placement.

Some studies evaluated diffusional changes in relation to severity of clinical symptoms and in relation to progression of symptoms (57). Decline in overall functionality, including mental status and stage of the disease, was related to altered diffusion in the lentiform nucleus and thalamus (57).

Razek *et al.* reported significant differences in putaminal diffusional values between 25 PD patients on levodopa treatment and 25 sex and age matched untreated PD patients and suggested that these differences could be attributed to the use of levodopa (58). However, other studies found no effect of levodopa treatment on FA or ADC values (49,59) and further studies are needed to elucidate the impact of antiparkinsonian treatment on diffusivity measures.

Diffusion-related measures have been correlated with cognitive performance in domains such as executive function, language, and attention (60). In addition, diffusion MRI has been used to get a better understanding of specific non-motor signs of PD.

Dementia in PD (PDD) frequently occurs in late disease stages and is associated with more rapid progression of disability and increased mortality (61). Reported fiber tracts involved in PDD patients include the (posterior) cingulate fiber tracts (62,63), corpus callosum (64), the superior and inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the uncinate fasciculus (65). Also, DTI has been used to study differences between DLB and PDD. In DLB more severely impaired bilateral posterior temporal, posterior cingular and visual association fibers have been reported (66).

Depression occurs in approximately 40% of PD patients and probably results in large part from the neurodegenerative changes occurring in PD (67). Results of a voxel based DTI study suggest a relationship between the mediodorsal thalamus and depressive symptoms (68). Another study did not find diffusional changes in PD with mild depressive symptoms, but did find reduced amygdale volumes (69). Because the study populations were relatively small and did not include healthy controls or patients with depression but without PD, these findings need additional validation.

Olfactory dysfunction is present in the majority of PD patients, even in the earliest pre-motor clinical stages (2). Several studies have reported decreased FA values or increased diffusivity values in the olfactory tract and the anterior olfactory region in early stage PD patients (70-72).

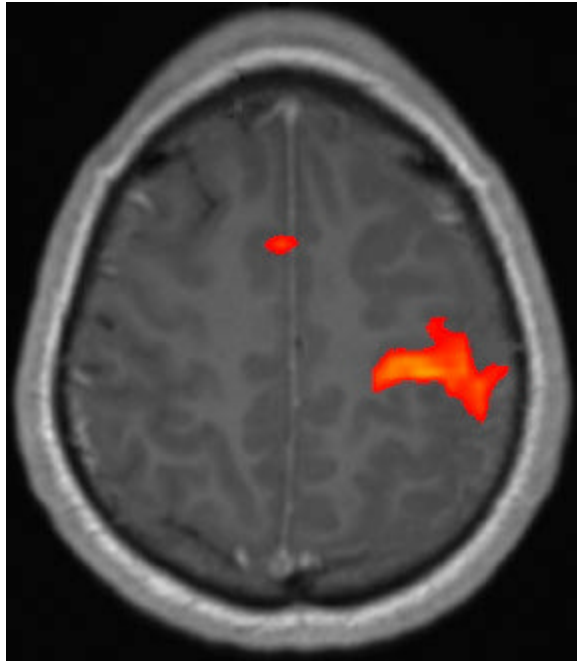


Figure 2. Blood-oxygen-level dependent (BOLD) functional MRI image in a patient performing the finger tapping motor task of the right hand. Activation of the left motor cortex is seen demonstrated by the orange overlay.

Diffusion MRI therefore seems to be able to detect both structural and functional neurodegenerative changes in the brain in early disease stages which to some extent correlate with clinical index scores. Although diffusion MRI is a promising new technique for application in clinical practice, standardization and validation of DTI acquisition, post-processing and diagnostic criteria is crucial and lacking at this time.

3.2.3. Magnetization transfer imaging

Magnetization transfer (MT) between free protons and protons bound to macromolecules is an indirect measure of tissue integrity. Neurodegenerative changes in MT as measured by magnetization transfer imaging (MTI) probably results from neural loss and gliosis. Pathologic MT changes in different brain structures have been detected with MTI, even when no evident atrophy or signal changes are seen on conventional brain MRI. Reported brain structures include the basal ganglia (73), paraventricular white matter, brain stem and SN (74-76). Also, MT changes in the olfactory cortex in PD has been reported (75). MT changes in these different brain structures in PD therefore seem to correlate with pathologic changes throughout the brain as we have seen in diffusion MRI as well. As MTI is reported to improve the visualization of neuromelanin, it seems to enable more accurate evaluation of the SNpc in PD (77,78).

In addition, MTI has been studied to differentiate between PD and AP. In their study Eckert *et al.* found good discrimination between PD, HC and AP (consisting of MSA and PSP), though differentiation between PD and HC and differentiation between MSA en PSP was insufficient (73).

At this point, the added value of MTI for more accurate diagnosis remains unclear.

3.2.4. Functional MRI

f-MRI relies on detecting changes in cerebral blood flow. Blood flow to a region of the brain increases when that region is functionally active. The primary form of f-MRI uses the Blood-oxygen-level dependent (BOLD) contrast (Figure 2). FMRI is used to map the brain to identify regions linked to critical functions such as speaking, moving, sensing, or planning but can also be used to study cognitive function. Another form f-MRI is resting state f-MRI (rs-fMRI), which enables visualization of intrinsic signal fluctuations in brain structures when a subject is not performing an explicit task. Rs-fMRI is used to evaluate regional interactions and functional connectivity. In PD, rs-fMRI is mainly used to evaluate functional connectivity of motor pathways.

In a systematic review, Herz *et al.* conclude that f-MRI to examine motor activation in PD shifts the focus from functional alterations at the cortical level to impaired activation in the basal ganglia (79), which is in line with findings of rs-fMRI in PD (80,81). Helmich *et al.* found decreased coupling between the posterior putamen and the inferior parietal cortex in PD (80). In contrast, the anterior putamen showed increased connectivity with the inferior parietal cortex, a finding that was interpreted as compensatory. These results suggest that dopamine depletion in PD leads to a remapping of cerebral connectivity that affects predominantly the sensorimotor circuit and sensorimotor integration (80). Changes in functional connectivity were also observed in relation to tremor in PD (81). The internal globus pallidus and putamen of tremor-dominant PD patients had increased functional connectivity in the cerebellothalamic circuit. Also, globus pallidus dopamine depletion correlated with clinical tremor severity. These results suggest that resting tremor might result from a pathological interaction between the basal ganglia and the cerebellothalamic circuit (81). Cortical changes in motor activation studied with fMRI are not consistent in terms of PD-related up- or down-regulation of regional cortical activity, and rely more strongly on the applied motor task (79).

4. PERSPECTIVES

As we have seen, conventional brain MRI sequences generally demonstrate limited abnormalities specific for PD and brain MRI in clinical practice is mainly used to exclude other pathology. In order to increase the diagnostic accuracy in early disease stages, a PD specific brain MRI diagnostic marker is desirable. Possibly, this can be provided by MRI scanners with higher magnetic field strengths, as illustrated by the identification of nigrosome1 on 7T brain MRI and its absence in PD. In other instances, higher magnetic field strengths can provide additional conflicting results. An example is the putaminal rim sign, considered to be suggestive of MSA on 1.5. T MRI and a normal finding on 3T MRI (82). Therefore, increase of MRI field strength does not guarantee the gain of new diagnostic markers. On the other hand, advanced MRI techniques

benefit from higher magnetic field strengths as it enables improved tissue contrast and increased temporal resolution.

Advanced MRI techniques hold promise to provide additional diagnostic markers for PD in early disease stages, as demonstrated by diffusional changes in the orbital-frontal region which are correlated with pre-motor phase of PD. The role of brain MRI in the pre-motor phase of PD needs to be further explored, as a very recent publication using MRI VBM and DTI did not find changes in Parkinson's disease related brain structures in a cohort of asymptomatic Parkinson disease-related gene mutation carriers (83). At this moment, identification of abnormal patterns of brain iron accumulation seems to be useful to identify AP instead of providing an additional diagnostic marker for PD.

Advanced imaging techniques have helped to explore and understand pathophysiologic changes in PD and AP by *in vivo* correlation between structural pathologic changes, functional connectivity and physical and cognitive functioning in a non-invasive manner, with a major role for the functional imaging techniques (DTI and F-MRI). A major drawback is that findings of group wise comparisons cannot be directly applied to clinical practice. A prerequisite for clinical application is standardized post processing and well defined imaging criteria, which are generally lacking for quantitative MRI techniques. Differences between MRI systems, scanning protocols and magnetic field strength should be assessed and taken into account when defining imaging criteria. As noted by Schwarz *et al.* for the SN (56), future studies should assess the influence of iron depositions on diffusional changes in brain structures and these should be correlated to age related physiological changes. Prospective clinical cohort studies are needed to evaluate the added diagnostic value of these new MRI techniques in relation to conventional brain MRI. Conducting such a study is challenging as obtaining histopathologic confirmation for larger study populations is practically impossible. Diagnosis based on a clinical follow-up of at least 2 years in the hands of a movement disorders specialist is therefore crucial to obtain silver standard diagnosis (11).

Positron emission tomography (PET) has been successfully employed to detect (preclinical) dopaminergic dysfunction in PD, to demonstrate therapy effect and to monitor disease progression (84). With the arrival of new hybrid imaging modalities, first experiences of combined PET/MRI scanners in parkinsonism can be expected in the near future which could possibly aid in determining diagnostic criteria for advanced MRI techniques.

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