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BRAIN WHITE MATTER CHANGESPRESENT IN PARKINSON'S DISEASE MADE VISIBLE THROUGH MAGNETIC RESONANCE IMAGING: AN INTEGRATIVE REVIEW

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ABSTRACT

Background: Parkinson's disease is a degenerative disease in which some brain structures are injured, requiring a technique that can analyze, in detail, grey and white matter in scans. This paper reports an integrative review undertaken to examine the scientific production related to cerebral white matter changes resulting from Parkinson's disease as identified through magnetic resonance imaging. Possible methods that can indicate disease progression in a clinically meaningful way. ***Method:*** This is a descriptive study of the integrative-review type in four databases from June and October 2017. Qualitative, quantitative and mixed-method studies were eligible for inclusion if they explored intermodal assessment, which included structural studies about magnetic resonance imaging and Parkinson's disease. ***Results:*** It was identified a total 4115 of articles. The analysis provided four thematic categories: (1) brain white matter changes in individuals with Parkinson's; (2) relationship between structural changes and the various damages caused; (3) differences present in brain scans of individuals with Parkinson's compared to other pathologies; and (4) the role of magnetic resonance imaging in Parkinson's disease. ***Conclusions:*** The advancement of imaging techniques allows an analysis of the anatomical aspects of the white matter in the brain. Magnetic resonance imaging can identify changes of cerebral white matter in patients with early-advanced Parkinson's disease by fractional anisotropy and increased mean diffusivity, mainly in the following areas: corpus callosum and the superior longitudinal fascicle. These changes may be associated with, for example, motor, cognitive, visual and olfactory impairment.

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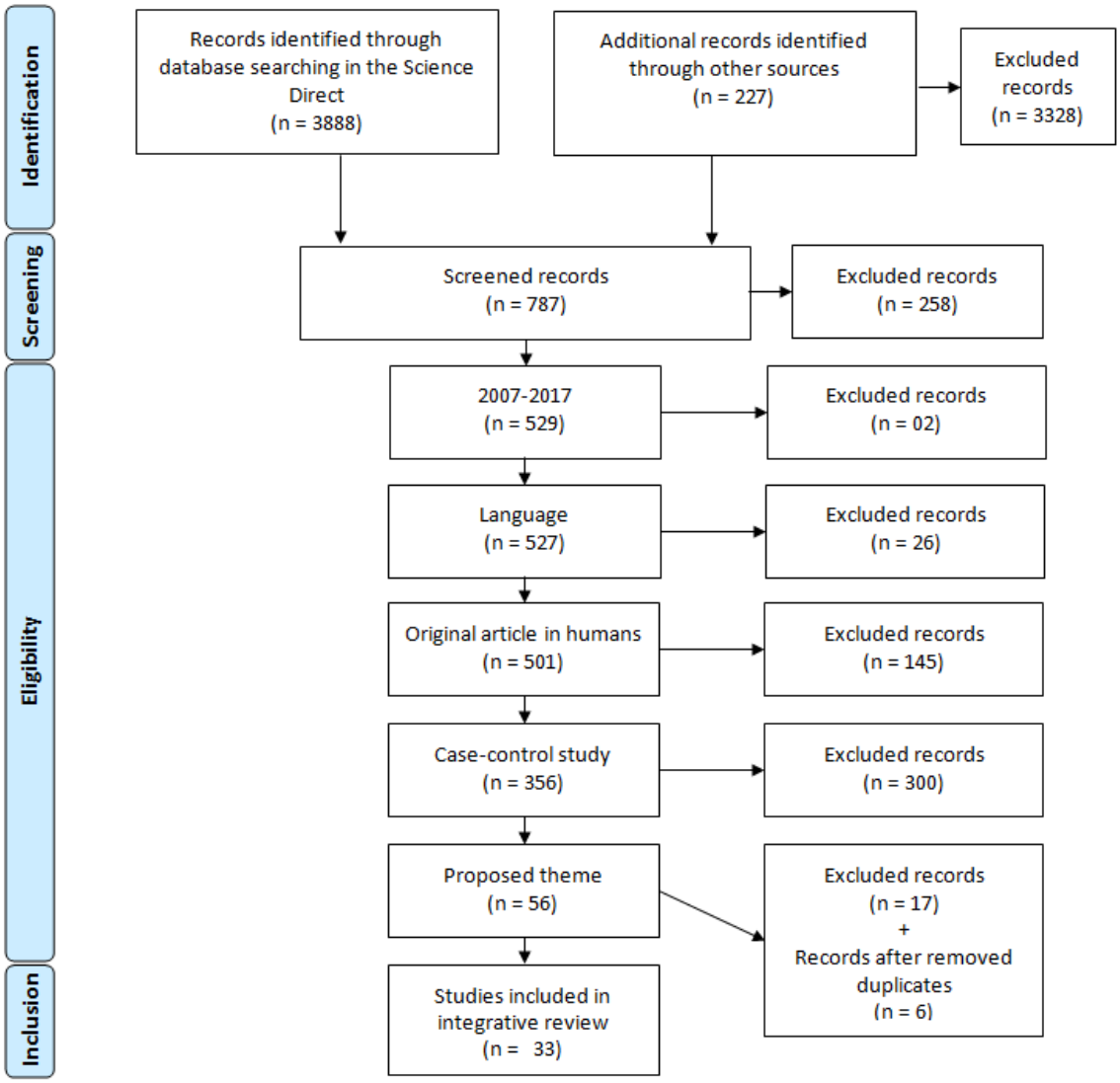
INTRODUCTION

Parkinson's disease (PD) is a degenerative disease and currently present in seven to nine million elderly citizens in the world (Lee, 2016), with anincreased growth of 3-5% in people aged over 85 years (Alves, 2008). Its diagnostic criteria are bradykinesia associated with resting tremorand/or stiffness, resulting from malfunctions in the nigrostriatal system.Studies have shown that the disease pathophysiology has a greater complexity, which may affect multiple systems, meaning that non-motor manifestations are also present (Postuma *et al.,* 2015; Kalia; Lang, 2015; Hall *et al.,* 2016; Domingo, 2015). PDinjures the brain structures, requiring a diagnostic technique that can analyzein detailthe grey and white matter (Osborn, 2010). Magnetic resonance imaging (MRI) provides diagnostic support andmakes it possible to identify lesions in these specific areas using high-resolution images (Teixeira, 2012; Zuiani, 2015).

Studies have sought to relate the reduction of the subcortical grey matter volume to early stages of PD (Lee *et al.*,, 2014), to identify the distribution of iron in the nervous system (Drayer *et al.,* 1986), and to compare the volume changes of grey and white matter (Tessa, 2008). Current reviews have identified, through MRI, the correlation between white matter lesions and motor (Veselý; Rektor, 2016; Bohnen; Albin, 2011) and cognitive deficits (Bohnen, 2011 and Duncan, 2012), in an attempt to understand their origin (Bohnen; Albin, 2011). Another study recently listed several techniques applied in MRI with structural and functional changes in PD, however, limited to the substantia nigra (Al-Radaideh; Rababah, 2016).This integrative review used a more comprehensive intermodal assessment, which included structural studies: longitudinal (T1 - weighted)and transversel (T2 - clinical) relaxation times, diffusion tensor imaging metrics (DTI), perfusion values, functional mode in magnetic resonance imaging (fMRI) and magnetization transfer (MTR). Thus, we



PRISMA 2009 Flow Diagram

were able toanalyze the scientific production related to cerebral white matter changes resulting from Parkinson's disease as identified through MRI, to better understand possible methods that canindicate disease progression in a clinically meaningful way.

MATERIAL AND METHODS

This is a descriptive study, of the integrative-review type, since it allows summarizing completed studies and achieving conclusions on a subject of interest by means of the analysis of significant studies for evidence-based practice, contributing to the deepening of knowledge and applicability (Beyea; Nicoll 1998). For methodological rigor, six steps were adopted in the preparation process (Mendes; Silveira; Galvão, 2008).

1st Step: Establishment of the research hypothesis or question: At first, the theme was set based on the study goal, brain white matter changes in individuals affected by PD, whose problems have relevance for both science and clinical practice. The keywords were then determined: "Parkinson disease", "Magnetic Resonance Imaging" and "white matter" for the survey of the literature. These were submitted with use of the Boolean operators AND or OR. All these keywords belong to the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MESH).

To guide the theme proposed in this review, the following research question was prepared: *What are the changes incerebral white matter resulting from the presence of Parkinson's visible through the magnetic resonance imaging?*

2ndStep: Search in the literature: The bibliographic survey was performed between June and October 2017. At this point, the following criteria were applied for inclusion in the search and selection of the sample in the literature, according to flow diagram 1: (1) publications between 2007-2017; (2) in English and/or Spanish and/or Portuguese; (3) original research with humans; (4) case-control studies; and (5) articles that discussed the proposed theme. As an exclusion criterion: (1) repeated articles among the databases.

The electronic search was performed through free electronic access to the Journal Portal of the Coordination for Higher Level Personnel Improvement (CAPES - *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*), in the following databases: PUBMED, Science Direct, Latin American and Caribbean Literature on Health Sciences (LILACS) and Medical Literature Analysis and Retrieval System Online (MEDLINE/EBSCO host).Thus, two researchers selected the articles independently, in order to ensure the reliability and validity of the study in question.

3rd Step: Categorization of studies: Two tables were prepared in order to organize and synthesize the information, based on the study reality. The first one contained the following topics: year, journal, title and results (Table 1). The second one addressed the study reference, the sample, the groups, sample size by groups, the scanner brand, the MRI technique, the sequence and the country (Table 2).

4th Step: Evaluation of studies included in the integrative review: The selected items that would compose the sample were then arranged in chronological order, starting with the most recent publications. Due to the objective of this study, articles with quantitative approach were used. Therefore, all articles were classified as level 3B of evidence (100%) (Howick, 2009), since they were case-controlled, which was one of the inclusion criteria.

5th Step: Interpretation of the results: In this step, the main findings in the literature on brain white matter changes in individuals affected by the PD were discussed, which allowed identifying gaps in the literature, as well as brain damaged areas, and the consequences associated with these changes.

6thStep: Presentation of the integrative review: The following presents the results of this integrative review descriptively.

RESULTS

The search returned 4,115 articles, submitted to the aforementioned inclusion and exclusion criteria, described in Flowchart 1. After applying these criteria, this integrative review included 33studies.The research design of all studies related toa single inclusion criterion, which stipulated the use of a quantitative approach through case-control study. These were found in the PUBMED, Science Direct, LILACS and MEDLINE/EBSCO host. Table 1 shows that most of the articles selected for the sample were recent, the years that stood out were: 2015, with nine articles; 2012, with five; and 2009 and 2016, each year with four. The remaining years of publication varied between one and three articles. Studies on the changes of cerebral white matter in patients with PD were published by various journals, the main ones presenting the following impact factors: 7.072, 3.54 and 5.835. Table 2 shows the size of the sample and groups, as well as the type of scanner, the MRI Technique, the imaging sequence and the country. The country of origin of the articles varied: 17 are from the European continent (Spain, Italy, United Kingdom, Belgium, Finland, Serbia, Germany, Poland, Denmark and Norway), eight are North American (Canada and United States), one from Oceania (New Zealand) and seven from Asia (China and South Korea). No article was found from the African continent. All articles were published in English.

Table 1. Synthesis of articles inserted in the integrative review according to year, journal, title and results. Recife, PE, Brazil, 2017

Year	Journal	Title	Results
2017	Clinical Radiology	Usefulness of diffusion-tensor MRI in the diagnosis of Parkinson's disease: a valuable tool to differentiate between them?	In the multiple system atrophy (MSA) group, the values of fractional anisotropy (FA) significantly decreased in the middle cerebellar peduncle, in the pontine crossing tract and in the corticospinal tract bilaterally. In the group of Parkinson's disease (PD), the FA values significantly decreased in multiple supratentorial areas, including corpus callosum, fornix and left hippocampus.
2017	Neurobiology of Aging	Cortical gray and subcortical white matter associations in Parkinson's disease	Twelve of the sixty-nine cortical subregions had significant differences in the group, and, for them, the underlying subcortical white matter was investigated. At baseline, the cortical volumes were correlated significantly with the underlying subcortical white matter axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA) (Ps ≤ 0.017) in PD. Lengthwise, higher rates of cortical atrophy in PD have been associated with increased rates of change of AD, RD and FA values (ps ≤ 0.0013) in both subregions.
2016	Movement Disorders	Gray and white matter imaging: a biomarker for cognitive impairment in early Parkinson's disease?	Increased mean diffusivity was observed bilaterally in subjects with PD, relative to controls (P = 0.019). Increased mean diffusivity was associated with performance on the semantic fluency and Tower of London tasks in frontal and parietal white matter tracts, including the cingulum, superior longitudinal fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus.
2016	NeuroImage: Clinical	Associations between mobility, cognition and callosal integrity in people with parkinsonism	The white matter network integrity reduced in people with frontal gait disorder and cognitive and gait deficits, which were exclusively related to interhemispheric circuits employed in the genu of the corpus callosum.
2016	PlosOne	Gray and white matter contributions to cognitive frontostriatal deficits in non-demented Parkinson's disease	Tract Based Spatial Statistics showed reduced prefrontal fractional anisotropy for Parkinson's disease relative to controls. Within Parkinson's disease, prefrontal fractional anisotropy and caudate nucleus volume partially explained processing speed. For controls, only prefrontal white matter was a significant contributor to processing speed. There were no significant anatomical predictors of working memory for either group.
2016	Psychiatry Research: Neuroimaging	Cortical abnormalities in Parkinson's disease patients and relationship to depression: A surface based morphometry study	Compared with non-depressed PD patients, depressed patients showed significantly increased cortical areas in the orbitofrontal regions and insula, which may imply white matter atrophy in these areas.
2015	Journal of Parkinson's Disease	Verbal Memory in Parkinson's Disease: A Combined DTI and fMRI Study	Compared to controls, PD patients showed verbal recognition memory impairment, lower fractional anisotropy in the anterior cingulate tract, and lower brain activation in the inferior orbitofrontal cortex.
2015	Human Brain Mapping	Brain structural and functional connectivity in Parkinson's disease with freezing of gait	PD-FoG patients showed WM damage of the PPT, corpus callosum, corticospinal tract, cingulum, superior longitudinal fasciculus, and WM underneath the primary motor, premotor, prefrontal, orbitofrontal, and inferior parietal cortices, bilaterally. In PD-FoG, right PTT damage was associated with a greater disease severity. Analysis on the independent PD sample showed similar findings in PD-FoG patients relative to controls as well as WM damage of the genu and body of the corpus callosum and right parietal WM in PD-FoG relative to PD no-FoG patients.
2015	European Neurology	Comparison of the brain volume in essential tremor and Parkinson's disease tremor using an automated segmentation method	Cerebellar atrophy of ET patients was more significant in the white matter than in the grey matter, and it was noted only in patients with ET having a head tremor. No volumetric differences were found between the PD group and the control group.
2015	European Journal of Radiology	Changes in anatomical and functional connectivity of Parkinson's disease patients according to cognitive status	In relation to the PD, the FA values found were significantly lower in the left PDD hippocampus. PDD showed high values of mean diffusivity (MD) in large areas of white matter when comparing PD and HC.

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2015	PlosOne	Neuroanatomical correlates of theory of mind deficit in Parkinson's disease: a multimodal imaging study	PD patients showed impairments in ToM, working memory and executive functions; grey matter loss and white matter reduction compared to healthy controls. Grey matter volume decrease in the precentral and postcentral gyrus, middle and inferior frontal gyrus correlated with ToM deficit in PD. White matter in the superior longitudinal fasciculus (adjacent to the parietal lobe) and white matter adjacent to the frontal lobe correlated with ToM impairment in PD. After controlling for executive functions, the relationship between ToM deficit and white matter remained significant for white matter areas adjacent to the precuneus and the parietal lobe.
2015	PlosOne	Tracking Parkinson's disease over one year with multimodal magnetic resonance imaging in a group of older patients with moderate disease	Using a voxel-based approach that focused on the centers of principal white matter tracts, the PD and control cohorts exhibited similar levels of change in DTI metrics. There was no significant change in perfusion, cognitive, or motor severity measures.
2015	Neuroscience	White matter differences between multiple system atrophy (parkinsonian type) and Parkinson's disease: a diffusion tensor image study	FA/RD values in bilateral corticospinal tract (CST) and left anterior thalamic radiation (ATR) in MSA-P were significantly different from PD or controls, and significantly correlated with clinical data.
2015	Movement Disorders	Microstructural changes in white matter associated with freezing of gait in Parkinson's disease	Tractography showed consistent white matter alterations in striatofrontal tracts through the putamen, caudate, pallidum, subthalamic nucleus, and in connections of the cerebellar peduncle with subthalamic nucleus and pedunculopontine nucleus bilaterally.
2014	Academic Radiology	Imaging Brain Iron and Diffusion Patterns: A Follow-up Study of Parkinson's Disease in the Initial Stages	The TBSS presented a small tendency to FA decrease ($P < 0.10$) in the genu of the corpus callosum and bilaterally in the corona radiata during the two years. The age of PD onset was cut at older than 67 years, revealing that those with earlier onset were associated with high FA values in large areas of peripheral white matter tract: bilaterally in frontal and parietal lobes and in the right side of the temporal and occipital lobe.
2014	NeuroImage	Mapping track density changes in nigrostriatal and extranigral pathways in Parkinson's disease	FD and MD values were not statistically significant according to the TBSS. However, the increased aerodynamic density in PD has been present in many areas of the cerebral white matter.
2014	Human Brain Mapping	Mild cognitive impairment in Parkinson's disease is associated with a distributed pattern of brain white matter damage	No region of WM damage was found in PD-Cu patients when compared with healthy controls. Relative to healthy controls and PD-Cu patients, PD-MCI patients showed a distributed pattern of WM abnormalities in the anterior and superior corona radiata, genu, and body of the corpus callosum, and anterior inferior fronto-occipital, uncinate, and superior longitudinal fasciculus, bilaterally. Subtle cognitive decline in PD is associated with abnormalities of frontal and interhemispheric WM connections, and not with GM atrophy.
2013	Movement Disorders	White matter abnormalities in Parkinson's disease patients with glucocerebrosidase gene mutations	Compared with controls, Parkinson's disease patients carrying glucocerebrosidase gene mutations showed decreased fractional anisotropy in the olfactory tracts, corpus callosum, and anterior limb of the internal capsule bilaterally, as well as in the right anterior external capsule, and left cingulum, parahippocampal tract, parietal portion of the superior longitudinal fasciculus, and occipital white matter. Mutation carrier patients also had decreased fractional anisotropy of the majority of white matter tracts compared with Parkinson's disease patients with no mutations. No white matter abnormalities were found in Parkinson's disease patients without glucocerebrosidase gene mutations. No gray matter difference was found between patients and controls. In Parkinson's disease patients, verbal fluency scores correlated with white matter abnormalities. Parkinson's disease patients carrying glucocerebrosidase gene mutations experience a distributed pattern of white matter abnormalities involving the interhemispheric, frontal corticocortical, and parahippocampal tracts.
2013	Journal of the International Neuropsychological Society	White matter microstructural integrity and executive function in Parkinson's disease	In Parkinson's patients, FA was related to executive composite scores, and both indices were related to Stroop interference scores.
2012	Movement Disorders	Color discrimination deficits in Parkinson's disease are related to cognitive impairment and white-matter alterations	Neuroimaging analysis revealed higher mean and radial diffusivity values in right posterior white-matter structures that correlated with poor performance on the Farnsworth-Munsell 100 hue test.
2012	NeuroImage	White matter pathology in Parkinson's disease: the effect of imaging protocol differences and relevance to executive function	The dataset with more gradient directions was more sensitive to reductions in fractional anisotropy in Parkinson's disease, whilst the dataset with more b values was more sensitive to increases in mean diffusivity. Moreover, the areas of reduced fractional anisotropy were highly similar to areas of increased mean diffusivity in PD patients. Next, we compared two widely used analysis methods: tract-based spatial statistics identified reduced fractional anisotropy and increased mean diffusivity in Parkinson's disease in many of the major white matter tracts in the frontal and parietal lobes. Voxel-based analyses were less sensitive, with similar patterns of white matter pathology observed only at liberal statistical thresholds. We also used tract-based spatial statistics to identify correlations between a test of executive function (phonemic fluency), fractional anisotropy and mean diffusivity in prefrontal white matter in both Parkinson's disease patients and controls.
2012	Journal of the Neurological Sciences	White matter lesions and depression in patients with Parkinson's disease	Comparing controls and PD patients as a group there were no differences in WMHs in any examined regions. However, PD-D group had more common frontal WMHs although WMHs score didn't rich statistical significance. The same came true for total deep white matter changes comparing those two groups. In addition PD-D group had a significantly higher score for periventricular regions WMHs comparing with both PD-nD group and controls. PD-D group had significantly higher WMHs scores BG regions when compared to controls. The only significance in multivariate analyses was shown for periventricular WMHs total score explaining the 39% of the variance in the depressive score.

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2012	Neurodegenerative Diseases	The impact of MRI white matter hyperintensities on dementia in Parkinson's disease in relation to the homocysteine level and other vascular risk factors	According to multivariate regression analysis, WMH (Erkinjuntti scale), high Hcy, low vitamin B12 and folate plasma levels were independent risk factors for PDD.
2012	Parkinsonism and Related Disorders	Intact limbic-prefrontal connections and reduced amygdala volumes in Parkinson's disease with mild depressive symptoms	The depressed PD group showed smaller amygdala volume compared to healthy controls, but the groups did not differ on any other measure, such as FA and MD.
2011	European Journal of Radiology	Voxel-based analysis of diffusion tensor indices in the brain in patients with Parkinson's disease	The damaged white and gray matter showed decreased FA or increased MD, localized bilaterally in the cerebellar and orbitofrontal cortex. In addition, in PD patients there was a positive correlation between FA values in the white matter of the left cerebellum and the thresholds of olfactory identification (TOI) and a negative correlation between MD values in the white matter of right cerebellum and the TOI.
2011	European Journal of Neurology	A magnetization transfer study of mild and advanced Parkinson's disease	Compared with controls, patients with PD1 exhibited a significant MTR reduction in substantia nigra pars compacta, substantia nigra pars reticulata, putamen, periventricular white matter and parietal white matter. In addition to the changes observed in PD1, the PD2 group exhibited a significant MTR reduction in caudate, pons, frontal white matter and lateral thalamus.
2011	American Journal Neuroradiology	Regional volume analysis of the Parkinson disease brain in early disease stage: gray matter, white matter, striatum, and thalamus	Comparison of the volumes of regional brain structures of patients with PD with those of controls revealed the presence of significant differences in the caudate nucleus, thalamus, and WM (P<.05) between the groups. However, there were no significant differences in the volumes of the putamen and GM or in ICV between patients with PD and controls. The results of ANCOVA by using the covariates of age and ICV showed a significant difference in the caudate nucleus, thalamus, and WM between patients with PD and controls (P<.05).
2010	European Journal of Neurology	A deformation-based morphometry study of patients with early-stage Parkinson's disease	The Deformation-Based Morphometry (DBM) comparison between patients and controls revealed significant contraction in the left cerebellum, and non-significant trends towards frontal, temporal and cingulate sulcal expansions with frontal and temporal white matter contractions. Within the patient group, the unified PD rating scores were highly correlated with local expansions in or near sulci bordering on frontal and temporal cortex.
2009	Movement Disorders	Temporal lobe changes in early, untreated Parkinson's disease	In PD, however, there was decreased WM volume in the anterior right fusiform gyrus and superior temporal gyrus. There were no correlations between the California Verbal Learning Test long delay free recall, Judgment of Line Orientation, Trail Making A or B and either the GM or WM localized volumes.
2009	NeuroImage	White matter hypertensities do not impact cognitive function in patients with newly diagnosed Parkinson's disease	Analysis showed that there were no significant differences between the 3 groups in total volume or spatial distribution of WMH. In addition there was no significant relationship between total volume or spatial distribution of WMH and attention-executive functions in PD.
2009	Movement Disorders	Brain atrophy and white matter hyperintensities in early Parkinson's disease	There was no evidence of brain atrophy or higher WMH volume in PD compared to NC, and MRI volumetric measurements were not significant predictors of cognitive functions in PD patients.
2009	American Journal Neuroradiology	White matter involvement in idiopathic Parkinson disease: a diffusion tensor imaging study	In patients, the MD was increased at borderline significance in the substantia nigra but was unaltered in the thalamus, globus pallidus, putamen, and in the head of the caudate nucleus. The FA and MD were unaltered in the corticospinal tract in the midbrain and at the level of the internal capsule, and in the splenium of the corpus callosum. By contrast, the MD was increased and the FA was decreased in the genu of the corpus callosum and in the superior longitudinal fasciculus; in the cingulum, only the MD was altered. The observed changes were not significantly lateralized.
2008	American Journal Neuroradiology	Altered diffusion in the frontal lobe in Parkinson disease	Decreased fractional anisotropy (FA) was observed in subjects with PD bilaterally in the frontal lobes, including the supplementary motor area, the presupplementary motor area, and the cingulum. There were no significant differences in mean diffusivity or GM/WM attenuation between PD and HC subjects.

Abbreviations: AD, axial; CHIPS, hyper-intensity scale of cholinergic pathways; LBD, Lewy bodies disease; ET, essential tremor; FA, fractional anisotropy; FC, functional connectivity; fMRI, functional magnetic resonance imaging; HC, healthy control; Hcy, homocysteine; ICV, intracranial volume; MD, mean diffusivity; MOCA, the Montreal cognitive assessment; MRI, magnetic resonance imaging; MSA, multiple system atrophy; MTL, Middle temporal lobe; PCC, posterior cingulate; MTR, magnetization transfer index; PD1, mild Parkinson's disease; PD2, advanced Parkinson's disease; PD, Parkinson's disease; PDD Parkinson's disease with dementia; PD-(D), Parkinson's disease with depression; PD-FoG, Parkinson's disease and freezing of gait; PD-MCI, Parkinson's disease with mild cognitive impairment; PPT, peduncle-pontino tract; RD, radial; SNc, substance nigra pars compacts; TBSS, tract-based spatial statistics; ToI, olfactory identification; ToM, theory of mind; UPDRS, unified Parkinson's disease rating scale; WMHs, white matter hyper-intensities.

Most studies presented the T1(25), followed by DTI (21) and T2 (11). Three studies used the fMRI and one used MTR. According to Table 3, when comparing the patient with PD with the healthy control (HC) through magnetic resonance imaging, the fractional anisotropy (FA) was shown to be significantly reduced in 15 studies, while eight studies did not show significant differences. With respect to the mean diffusivity (MD), nine studies showed significant increase, seven had no significant results and seven studies did not analyze this variable. The FA and the MD were evaluated in 10 sample studies. Table 3 shows the affected brain areas. In Table 4, the volume of white matter in the PD group when compared to the HC shows divergent results: in three studies, the volume of white matter in the PD group was reduced (Lee *et al.,* 2011; Dalaker *et al.,* 2009; Surdhar *et al*. 2012), while, in two others, it increased (Martin *et al.,* 2009; Choi *et al.,* 2015).

With respect to brain volume, there was a greater loss in the group affected by the PD when compared to the HC after 12 months (Melzer *et al.,* 2015). The detection of white matter hyper intensity was made using automation and showed no significant difference between PD and HC (Dalaker *et al.,*2009). In addition, similar results also occurred in other studies when using manually applied scales, like those proposed by Scheltens (Petrovic *et al.,* 2012; Sławek *et al.,* 2013), Wahlund (Sławek *et al.,* 2013) and Erkinjunntti (Sławek *et al.,* 2013).Transversel relaxation was also seen to be increasedthe globus pallidus anterior, which was more significant, andin the caudate nucleus over time in all three sequences when the baseline was compared with 2-year follow-up of PD patients (Rossi *et al.,* 2014).Only one study showed results related to MTR, which compared patients with Parkinson's disease in the early (PD1) and advanced (PD2) stages with the HC.

Table 2. Synthesis of the sample data of the articles inserted in the integrative review. Recife, PE, Brazil, 2017

Study	Sample	Groups	Size	Scanner	MRI	Sequence	Country
Chen et al. 2017 [59]	62	PD HC MSA	18 24 20	GE	3 T	DTI	China
Sterling et al. 2017 [32]	146	PD HC	76 70	Siemens	3 T	DTI T1	United States
Duncan et al. 2016 [38]	175	PD HC	125 50	Philips	3 T	DTI T1	United Kingdom
Fling et al. 2016 [42]	30	PD HC FDG	10 10 10	Siemens	3 T	DTI T1 HARDI	United States
Price et al. 2016 [53]	80	PD HC	40 40	Siemens	3 T	DTI T1 T2 FLAIR	United States
Huang et al. 2016 [58]	79	PD HC PD-D	17 45 17	GE	3 T	T1 Fast spoiled gradient recalled echo sequence	China
Lucas-Jiménez et al. 2015 [54]	52	PD HC	37 15	Philips	3 T	DTI fMRI EPI T1	Spain
Canu et al. 2015 [35]	57	PD-FoG HC	23 35	Philips	3 T	DTI fMRI T1 T2 FLAIR	Italy
Choi et al. 2015 [24]	135	PD HC TE	45 45 45	GE	1,5 T	T1 T2 FLAIR	South Korea
Chen et al. 2015 [50]	51	PD HC PDD	19 21 11	GE	3 T	DTI fMRI T1	China
Díez-Cirarda et al. 2015 [63]	52	PD HC	37 15	Philips	3 T	DTI T1	Spain
Melzer et al. 2015 [25]	46	PD HC	23 23	GE	3 T	DTI T1 T2 FLAIR	New Zealand
Ji et al. 2015 [60]	55	PD HC MSA	20 20 15	Siemens	3 T	DTI T1 T2	China
Vercruysse et al. 2015 [64]	42	PD HC PD-FoG	15 15 11	Siemens	3 T	DTI	Belgium
Rossi et al. 2014 [28]	44	PD HC	25 19	Siemens	3 T	T2 T2 Mapping* SWI	Finland
Ziegler et al. 2014 [43]	53	PD HC	27 26	Siemens	3 T	DWI FLASH T1	Belgium
Agosta et al. 2014 [46]	76	PD HC PD-MCI	13 33 30	Siemens	1,5 T	DTI T1 DE	Serbia
Agosta et al. 2013 [44]	45	PD HC GBA-PD	14 16 15	Siemens	1,5 T	DTI T1 DE SE	Germany
Gallagher et al. 2013 [45]	30	PD HC	15 15	GE		DTI T1 FLAIR	United States
Bertrand et al. 2012 [56]	86	PD HC PD-MCI	31 20 35	Siemens	3 T	DTI T1	Canada
Rae et al. 2012 [49]	29	PD HC	14 15	Siemens	3 T	DTI	United Kingdom
Petrovic et al. 2012 [26]	89	PD HC PD-D	25 30 34	Siemens	1,5 T	T1 TSE FLAIR	Serbia
Slawek et al. 2012 [27]	376	PD HC	192 184	-	1,5 T	T2	Poland
Surdhar et al. 2012 [22]	18	PD HC PDD	6 6 6	Siemens	1,5 T	DTI T1 T2 FLAIR	Canada

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Zhang et al. 2011 [57]	50	PD HC	25 25	Siemens	3 T	DTI	China
Tambasco et al. 2011 [29]	32	PD1 PD2 HC	11 11 10	GE	1,5 T	MTR T1 T2	Italy
Lee et al. 2011 [20]	30	PD HC	15 15	Philips	1,5 T	T1	South Korea
Borghammer et al. 2010 [62]	50	PD HC	24 26	GE	3 T	T1	Denmark
Martin et al. 2009 [23]	40	PD HC	26 14	Siemens	1,5 T	T1	Canada
Dalaker et al. 2009 [21]	265	PD HC PD-MCI	133 102 30	Philips	1 e 1,5 T	FLAIR	Norway
Dalaker et al. 2009 [41]	256	PD HC	155 101	Philips	1 e 1,5 T	T1 FLAIR	Norway
Gattellaro et al. 2009 [30]	20	PD HC	10 10	Siemens	1,5 T	DTI T2	Italy
Kendi et al. 2008 [65]	25	PD HC	12 13	Siemens	3 T	DTI T1	United States

Abbreviations: DE, Double Eco; DTI, diffusion tensor image; DWI, diffusion-weighted image; FGD, frontal gait disorder; FLAIR, fluid attenuated inversion recovery; fMRI, functional magnetic resonance imaging; GBA-PD, Parkinson's disease with the glucocerebrosidase gene; GE, general electric; HARDI, diffusion images with high angular resolution; HC, healthy control; MRI, magnetic resonance imaging; MSA, multiple system atrophy; MTR, magnetization transfer; PD1, mild Parkinson's disease; PD2, advanced Parkinson's disease; PD, Parkinson's disease; PDD Parkinson's disease with dementia; PD-D, Parkinson's disease with depression; PD-FoG, Parkinson's disease and freezing of gait; PD-MCI, Parkinson's disease with mild cognitive impairment; SE, SpinEco; SWI, probability-weighted mean; ET, essential tremor; TSE, Pulse turbo spin echo.

Table 3. Structural alterations of cerebral white matter related to fractional anisotropy and mean diffusivity in individuals with Parkinson's disease when compared to the healthy control group. Recife/PE, Brazil, 2017

Study	↓FA	Places	↑MD	Places
Chen et al. 2017 [59]	+	Body of the corpus callosum, fornix, L hippocampus and L inferior frontal-occipital fasciculus.	-	-
Sterling et al. 2017 [32]	+	Total volume of the cerebral cortex.	-	-
Duncan et al. 2016 [38]	NS	-	+	Parietal and frontal subcortical tract, bilaterally; including forceps minor; cingulate; upper and lower longitudinal fasciculus; lower frontal-occipital fasciculus, cortical-spinal tract, corpus callosum and internal capsule.
Fling et al. 2016 [42]	+	Inter-hemispheric primary somatosensory fibers tract.	+	All inter-hemispheric sensorimotor fiber tracts of the corpus callosum.
Price et al. 2016 [53]	+	Corpus callosum (genu and body), forceps minor, anterior thalamic radiations, portions of inferior frontal-occipital fasciculus and uncinate fasciculus.	-	-
Huang et al. 2016 [58]	-	-	-	-
Lucas-Jiménez et al. 2015 [54]	+	L anterior cingulate tract.	-	-
Canu et al. 2015 [35]	+	Primary motor, premotor, prefrontal, orbitofrontal, and inferior parietal cortices; cingulum and superior longitudinal fasciculus bilaterally, cerebral peduncles, corpus callosum (genu, anterior body and splenium), temporal-occipital white matter tract, bilateral.	+	Primary motor, premotor, prefrontal, orbitofrontal, and inferior parietal cortices; cingulum and superior longitudinal fasciculus bilaterally, cerebral peduncles, thalamic radiations, external capsule, bilaterally, and cerebellum.
Choi et al. 2015 [24]	-	-	-	-
Chen et al. 2015 [50]	NS	-	NS	-
Díez-Cirarda et al. 2015 [63]	+	Right uncinate fasciculus adjacent to the insular cortex and frontal lobe.	NS	-
Melzer et al. 2015 [25]	+	Genu, body and splenium of the corpus callosum, cingulate gyrus, superior corona radiate and the posterior portions of the multiple fasciculus.	+	Right superior corona radiata.
Ji et al. 2015 [60]	NS	-	NS	-
Vercruysse et al. 2015 [64]	+	L cerebellar hemisphere, L temporal part of superior longitudinal fasciculus.	+	R anterior part of the inner capsula and corona radiata, superior frontal cortex, L cerebellar hemisphere.
Rossi et al. 2014 [28]	+/-	Genu of the corpus callosum and anterior corona radiata, bilateral.	-	-
Ziegler et al. 2014 [43]	NS	-	NS	-
Agosta et al. 2014 [46]	NS	-	NS	-
Agosta et al. 2013 [44]	NS	-	NS	-
Gallagher et al. 2013 [45]	+	R midbrain, frontal, temporal, parietal and occipital gyrus.	+	-
Bertrand et al. 2012 [56]	NS	-	+	Temporal and parietal portion of R inferior longitudinal fasciculus.

…….Continue

Rae et al. 2012 [49]	+	Prefrontal, temporal and parietal, corpus callosum and superior corticospinal tract.	+	Prefrontal, parietal and temporal, medial and inferior corticospinal tract, internal and external capsules, and corpus callosum.
Petrovic et al. 2012 [26]	-	-	-	-
Slawek et al. 2012 [27]	-	-	-	-
Surdhar et al. 2012 [22]	NS	-	NS	-
Zhang et al. 2011 [57]	+	Cerebellum, R rectus gyrus.	+	Bilateral orbitofrontal cortices, inferior temporal gyrus.
Tambasco et al. 2011 [29]	-	-	-	-
Lee et al. 2011 [20]	-	-	-	-
Borghammer et al. 2010 [62]	-	-	-	-
Martin et al. 2009 [23]	-	-	-	-
Dalaker et al. 2009 [21]	-	-	-	-
Dalaker et al. 2009 [41]	-	-	-	-
Gattellaro et al. 2009 [30]	+	Genu of corpus callosum and superior longitudinal fasciculus.	+	Genu of the corpus callosum and superior longitudinal fasciculus, cingulate.
Kendi et al. 2008 [65]	+	Medial frontal cortex, including the supplementary motor area; the presupplementary motor area; the R rostral medial frontal gyrus; the L anterior cingulate gyrus; L and R rostral cingulate gyrus; the R superior, middle, and inferior grontal gyrus; and the bilateral middle frontal gyrus at the frontal pole.	-	-

Abbreviations: +, present; -, absent; CC, corpus callosum; FA, fractional anisotropy; L, left; MD, mean diffusivity; NS, no significant difference; R, right.

Table 4. White matter volume in subjects with Parkinson's disease when compared to the healthy control group. Recife/PE, Brazil, 2017

Study	Volume		*p*-value	Observations
	PD	HC		
Choi et al. 2015 [24]	452 +/- 71.9 ml	450.2 +/- 47.5 mL	0.989	There was no significant difference between the volume of the white matter.
Surdhar et al. 2012 [22]	0.49 (0.0) SD	0.5 (0.1) SD	0.43	Significant difference in amygdala.
Lee et al. 2011 [20]	354 +/- 39.8 cm^3	396 +/- 28.6 cm^3	0.003	Reduction of 2.23% of white matter compared to HC.
Dalaker et al. 2009 [21]	662.1 +/- 40.0 ml	672.0 +/- 38.4 mL	0.285	There was no difference between PD and HC.
Martin et al. 2009 [23]	469 +/- 55 ml	447 +/- 53 mL	<0.05	There was no significant difference in overall brain volume and white matter. Local decrease in white matter volume in the right temporal lobe, more specifically in the right superior temporal gyrus and right fusiform gyrus.

Abbreviations: PD, Parkinson's disease; HC, healthy control group.

In accordance with the Bonferroni test, the MTR values were significantly reduced in the group affected by the PD in periventricular and parietal white matter. When compared, the PD1 presented reduced MTR of the white matter in the centrum semiovalis and parietal areas. The PD1 showed increased MTR when compared to PD2 paraventricular and frontal white matter. The HC, when compared to the PD1 and PD2, presented higher MTR values in all aforementioned white matter areas (Tambasco *et al.,* 2011).

DISCUSSION

After full analysis of articles that composed the sample of this integrative review, four thematic categories emerged, namely: (1) brain white matter changes in individuals with Parkinson's; (2) relationship between structural changes and the various damages causes; (3) differences present in Parkinson's compared to other pathologies; and (4) the role of magnetic resonance imaging in the diagnosis and treatment of Parkinson's disease. Below is a description of what was found in the literature search.

Brain white matter changes in individuals with Parkinson's

Micro-structural changes in the PD without dementia can be observed in the genu of the corpus callosum, in the superior longitudinal fasciculus and in the cingulate gyrus (Gattellaro *et al.,* 2009). These ganglia or basal nuclei, composed of the substantianigra (pars compacta and cross-linked), striatum (caudate and putamen), globus pallidus (internal and external) and subthalamic nucleusare responsible for controlling voluntary movements (Burch; Sheerin, 2005).Over time, however, cortical atrophy can occur, and the diffusion of the subcortical white matter can change, in both people with PD and HC (Sterling *et al.,* 2017) since the nervous system is subjected to various anatomical and physiologicalchanges, such as reduced volume of the cerebral cortex (Storvse *et al.,* 2014), which, in turn, can occur in PD (Lewis, 2016). Regarding the connections involved in white matter damage, there is a greater distribution involving the fronto-parietal, temporo-occipital and cortico-cortical connections, as well as the genu and the splenium of the corpus callosum (Canu *et al.,* 2015). The reduced volume of white matter in the PD group is also notable, when compared with the HC, as it can occur from the earliest stages, affecting the caudate nucleus and the thalamus (Lee *et al.,* 2011), or even the right temporal lobe (Martin, 2009). The thalamus comprises motor, cognitive and limbic aspects that are responsible for various motor and non-motor symptoms in the PD (Lewis; Barker,2009). Furthermore, there is a high prevalence of white matterhyperintensity (Dalaker *et al.,* 2009), which suggests the presence of tissue damage, which may be related to demyelination in different degrees or even with cognitive and behavioral changes, for example (Teixeira, 2012;Veselý; Recktor, 2016). It can also indicate the axonal loss/damage (Gouw *et al.,* 2011 and Duncan, 2016) as well as the association between the left postcentral gyrus atrophy and increased FA (Sterling, 2017). There is a distributed pattern of

white matter damage involving extra-motor and sensory-motor pathways that involves patients with PD and gait alterations (Canu *et al.,* 2015). In the magnetization transfer, the putamen was seen to be reduced in the group with mild PD, while in advanced PD, the caudate nucleus and the lateral thalamus were reduced (Tambasco *et al.,* 2011). Other studies have also shown a decline in the average MTR in specific brain areas such as the globus pallidus and the periventricular white matter even in early stages (Eckert *et al.,* 2004; Anik *et al.,* 2007). Therefore, there may be a variance related to the amendments scope, as well as the areas involved, depending on the PD progress. However, global structural changes in the brain are not seen to be important in a patient with PD diagnosed early (Dalaker *et al.,* 2009).

Relationship between structural changes andcauses of brain damage: Formerly, the mainbrain damage inPDwas thought to be in the motor area. Thus, the impact on locomotory performance was also related to white matter changes in the genu of the corpus callosum, which suggests an interruption of inter-hemispheric communication of the prefrontal cortex (Fling *et al.,* 2016).Gait freezing results from a low structural and functional integration between the motor nervous and cognitive systems (Canu *et al.,* 2015).Nevertheless, PD is also associated with non-motor symptoms, as there is a connection between walking and cognition (Fling *et al.,* 2016),making it to possible to observe the damage to the cognitive area as correlated with the grey and white matter in newly-identified PD patients (Duncan *et al.,* 2016), and white matter tract damage (Ziegler *et al.,* 2014; Agosta *et al.,* 2013; Gallagher *et al.,* 2013), frontal and frontoparietal that connect cortical and subcortical structures (Agosta *et al.,* 2014). This enables perception of the presence of cognitive impairment in the PD (Melzer *et al.,* 2013) and how changes in white matter influencedamage, as well as behavioral manifestations (Agosta *et al.,* 2013; Hattori *et al.,* 2012; Rae *et al.,* 2012). Cognitive decline may be associated with the functional connectivity of the right posterior cingulate cortex of the medial temporal lobe (Chen *et al.,* 2015), which may indicate an early start of the PD when related to degeneration of the integrity of the white matter tract, which is identified by means of increased MD and absence of significant reduction in FA (Duncan *et al.,* 2016).

The MD is related to a directionally independent measure (Norris, 2001). The FA measures the ratio of the water diffusion and reflects the consistency of directional alignment of fibers in the white matter tracts (Rae *et al.,* 2012), which reflect the degree of myelination, axonal density, and interstitial space, among others (Norris, 2001; Le Bihan *et al.,* 2001).Associated to cognition, processing speed improves with increased FA in the white matter (Price *et al.,* 2016), and verbal learning. There is a significant positive correlation between brain activation and lower frontal-orbit cortex during specific tasks for this function in the fMRI and FA of the uncinate fasciculus (Lucas-Jiménez *et al.,* 2015). Moreover, there is a significant decrease in FA values and increased MD in white matter fibers in the PD due to the micro-structural changes (Melzer *et al.,* 2013).Other factors may interfere with the PD individual's cognition, such as white matter hyperintensitiesin conjunction with homocysteine, folate and vitamin B12 (Sławek *et al.,* 2013). Non-motor symptoms are also associated with other senses such as vision and smell. In case of deficit in discrimination of colors, identified through the Farnsworth-Munsell100 shades test, cognitive deficiencies can be identified. In addition poor performance may demonstrate an association with white matter changes in posterior and right brain regions (Bertrand *et al.,* 2012).Olfactory dysfunction has already been confirmed as a clinical sign for early PD (Zhang *et al.,* 2011).

Differences present in Parkinson's compared to other pathologies

In order to perform a differential diagnosis, some studies have compared pathologies thatmay have similar signs and symptoms, causing insecurity when diagnosing PD, as observed for mild cognitive impairment. In this case, faster changes in eachglobus pallidus anterior, compact substantia nigra and cerebral peduncle were foreseen (Rossi *et al.,* 2014),are seen to be associated with white frontal-parietal, frontal-temporal and inter-hemispheric white matter tract damage, and not with atrophy of gray matter (Agosta *et al.,* 2014).The PD association with dementia, compared to the HC, showed significant MD values higher in the splenium and body of the corpus callosum, right superior frontal-occipital fasciculus, left inferior longitudinal fasciculus and bilateral uncinate fasciculus, thus, a widespread change (Chen *et al.,* 2015).In addition to this cortical increase, bilateral amygdala atrophy (Surdhar *et al.,* 2012) suggests that these changes may contribute to a clinical picture of depression (Huang, 2016). Furthermore, these verity of the depression correlates significantly with the total score of the periventricular white matter hyperintensity (Petrovic, 2012).The cortical increase in the orbit-frontal area in PD patients with depressionis evident. This increase, associated with insula's increase, can contribute to reduce the volume of white matter, the deeper grooves and extended surface area resulting from the tension or shrinkage of these fibers (Huang *et al.,* 2016).The multiple system atrophy (MSA), when compared with the PD group, showed reduced FA in medium cerebellar peduncle, in the pontine crossingtract, cortico-spinal tract (Chen *et al.,* 2017) and left thalamic radiation (Ji *et al.,* 2015). However, another study used the FA values in the body of the corpus callosum to differentiate patients with MSA from PD patients (Chen *et al.,* 2017). Therefore, these points seem to contribute to a differential diagnosis and to be useful for evaluating MSA progression (Ji *et al.,* 2015). Patients affected by essential tremor (ET), when compared to PD patients, presented cerebellar atrophy in the white matter (Choi *et al.,* 2015), even damage (Zhang *et al.,* 2011), which can contribute to the differentiation between these diseases by brain segmentation (Choi *et al.,* 2015) because the cerebellum is also responsible for adjusting the limb in relation to position and time (Yousry *et al.,* 2001).

The role of magnetic resonance imaging in the diagnosis and treatment of Parkinson's disease: Magnetic resonance imaging presents a potential role as a biomarker of PD associated with cognitive function due to the measurement of white matter integrity, as well enabling an estimate of the volume of grey matter (Duncan *et al.,* 2016). Other analytical methods may be sensitive to assess morphological changes, such as deformation-based morphometry (Borghammer *et al.,* 2010).The combination of fMRI methods with DTI can enable early identification of dementia in PD due to neuronal and white matter changes (Agosta *et al.,* 2013; Chen *et al.,* 2015). However, the use of MRI can also contribute to a differential diagnosis between PD and its variants, like MSA (Chen *et al.,* 2017). It can even help differentiate from other pathologies

that have some similarity in signs and symptoms, such as ET (Lucas-Jiménez *et al.,* 2015).This integrative review was restricted to only one type of case-control study. Future studies should cover other types of studiesin order to present a global approach of the anatomical changes of white matter. Moreover, a multimodal perspective should be used, encompassing other assessment methods in individuals affected by PD.

Conclusion

The advancement of imaging techniques enables analysis of the anatomical structure of the cerebral white matter. MRI can identify changes of cerebral white matter in patients with early-advanced PD through reduced FA and increased MD mainly in the following areas: corpus callosum, superior longitudinal fascicle. These changes might be associated with, for example, motor, cognitive, visual and olfactory impairment. Thus, magnetic resonance imaging emerges as an important instrument for clinical practice, either as a predictor of PD, or even as a tool to differentiate it from other pathologies, and identify the level of damage, as well as the evolution of the PD itself.

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