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MRI and Cognitive Impairment in Parkinson's Disease

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Abstract: Patients with Parkinson's disease (PD) may present impairment in cognitive functions even at early stages of the disease. When compared with the general population, their risk of dementia is five to six times higher. Recent investigations using structural MRI have shown that dementia in PD is related to cortical structural changes and that specific cognitive dysfunctions can be attributed to atrophy in specific structures. We review the structural MRI studies carried out in PD using either a manual region of interest (ROI) approach or voxel-based morphometry (VBM). ROI studies have shown that hippocampal volume is decreased in patients with PD with and without dementia; in addition, hippocampal atrophy correlated with deficits in verbal memory. VBM studies have demonstrated that dementia in PD involves structural changes in limbic areas and widespread cortical atrophy. Findings in nondemented patients with PD are less conclusive, possibly because cognitively heterogeneous groups of patients have been studied. Patients with PD with cognitive impairment and/or visual hallucinations present greater brain atrophy than patients without these characteristics. These findings suggest that cortical atrophy is related to cognitive dysfunction in PD and precedes the development of dementia. Structural MRI might therefore provide an early marker for dementia in PD. © 2009 Movement Disorder Society

Key words: Parkinson's disease; dementia; hallucinations; MRI; cognitive functions

Parkinson's disease (PD) has traditionally been considered as a motor disorder. However, cognitive dysfunctions are known to occur even at early stages[1] and most patients develop dementia over the course of the disease.[2] Dementia in PD was initially described as subcortical, and cognitive dysfunctions in nondemented patients have been attributed to dopaminergic depletion affecting the fronto-striatal circuit[3] or the dopamine-acetylcholine synaptic imbalance.[4] Nevertheless, recent investigations using MRI suggest that specific cognitive deficits, such as memory deficits, and dementia in PD may also be explained by cortical structural changes. The methods most widely used to assess structural MRI changes in PD have been region of interest (ROI) and voxel-based morphometry (VBM). The ROI method consists in measuring manually delineated and anatomically defined regions within the brain based on an a priori hypothesis. ROI approach takes into consideration the variability across subjects, but as it also depends on the subjective criteria of the investigator, time-consuming inter and intrarater validations are mandatory. VBM is a fully automated whole brain measurement technique that maps the statistical probability of differences in regional tissue volume or density between groups.[5] It provides a nonbiased measure of regions that may be neglected in hypothesis-based studies using ROI. However, the normalization stage within the VBM analysis, which is required to ensure that the same brain regions can be

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compared between subjects, transforms the shape of the brain image and may distort the abnormal tissue and artificially inflate the atrophied areas.[6] Other structural techniques that have proved successful in detecting atrophy are surface-based and 3D-modeling analyses,[7,8] but they have not been used to date in PD.

In this study, we review structural MRI findings using manual ROI and VBM in patients with PD with dementia, patients with PD without dementia, and nondemented patients with PD with neuropsychological impairment and/or hallucinations who are therefore at risk of developing dementia.

MRI STUDIES IN PATIENTS WITH PD WITH DEMENTIA

Manual ROI studies in patients with PD have mainly focused on medial temporal lobe structures because these areas are known to present atrophy in other dementias such as Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) and because differences in the degree of atrophy between dementias may have important implications for diagnosis.[9,10] Atrophy of the hippocampus[11–14] and amygdala[13,14] has been reported in PD with dementia, remaining statistically significant after controlling for global cerebral volume. In addition, reduced entorhinal cortex volume has been reported in patients with PD with dementia when compared with controls.[15] Medial temporal lobe atrophy is encountered in AD,[16] but studies in PD with dementia show that atrophy in medial temporal lobe areas may also underlie dementia in PD.

In a previous study using VBM, we observed that patients with PD with dementia showed gray matter loss in hippocampus, parahippocampus, and anterior cingulate gyrus as well as the basal ganglia in comparison with healthy controls.[17] Interestingly, the hippocampus[18,19] and cingulate gyrus[20,21] are known to be major targets for Lewy body (LB) inclusions in PD. Another VBM study with a large number of patients provided further evidence of medial temporal and basal ganglia atrophy, but also reported greater widespread neocortical atrophy.[22] In that study, atrophy of the medial temporal lobe structures was more pronounced in AD than in demented PD and there were no differences between DLB and PD with dementia. However, another group has recently reported that patients with DLB showed greater neocortical atrophy than patients with PD with dementia in the temporal, parietal, and occipital lobes.[23]

The degree of atrophy in demented patients with PD may vary depending on the time of the occurrence of dementia in the course of the disease (i.e., early or late).[24] Early development of dementia has been associated with more severe degeneration of cortical and subcortical structures in neuropathological[25] and neuroimaging studies.[24] Overall, neuroimaging studies are in agreement with findings in postmortem neuropathological studies in demented PD, which report morphological changes in limbic[18,19] and neocortical areas[19–21] and have the advantage of assessing these changes in vivo. The fact that changes in medial temporal lobe areas are common to dementia in PD and to other neurodegenerative diseases such as AD and DLB raises the question of whether AD or cortical LB type changes underlie cognitive dysfunctions in PD[26]; unfortunately, the structural MRI neuroimaging techniques reviewed in this work are still some way from resolving this matter.

MRI STUDIES IN PATIENTS WITH PD WITHOUT DEMENTIA

The first study using a manual ROI approach[11] to assess the hippocampus in nondemented patients with PD reported decreased hippocampal volume in patients with PD without dementia when compared with controls. However, these results should be viewed with caution, because some patients may have met criteria for mild cognitive impairment (MCI), but it was not detected. Another study[12] looked for differences in several structures including the hippocampus, parahippocampus, temporal lobe, frontal lobe, and parietooccipital areas, finding that only corrected hippocampal volumes differed in nondemented patients with PD and controls ($P = 0.004$), even though the effect size for nondemented patients with PD was only 0.66 when compared with effect sizes of 1.22 and 1.81 for demented PD and AD groups, respectively. It has also been reported that nondemented patients with PD presented volume reductions of 11% in the amygdala and 10% in the hippocampus when compared with controls; volumes of both structures in nondemented patients with PD had values between those of demented patients and controls, although the differences did not reach statistical significance.[13] In addition, significant age-associated hippocampal atrophy in PD was found in one study in which hippocampal volumes in old (>70) nondemented patients differed from controls, but not in younger cases.[14]

Studies using visual evaluation of atrophy[27] in PD, in which a score of zero represented absence of atrophy and a score of four high severity, reported that early stage nonmedicated patients with PD had atrophy

in the bilateral prefrontal cortex and hippocampus. The right hippocampus atrophy score was 1.15 in PD versus 0.45 in controls, and the left hippocampus score was 1.05 in PD versus 0.64 in controls.[28] Another study from the same group[29] in a sample of nondemented patients with PD but at a more advanced stage of the disease and with impairment in several cognitive domains also reported atrophy in the hippocampus and the prefrontal cortex when compared with controls. Rated visually, more severe medial temporal atrophy has also been reported in patients with PD versus controls, but less than in subjects with DLB and AD.[30]

Results of VBM studies in patients with PD without dementia are heterogeneous, but most findings suggest the involvement of neocortical areas. In these patients, atrophy has been reported in caudate nucleus,[31] frontal areas and insula,[22] prefrontal cortex and parahippocampus,[32] hippocampus and anterior cingulate,[17] left intraparietal sulcus,[33] superior temporal and frontal gyrus,[34,35] and cerebellum.[36] A possible explanation for this high variability might be the heterogeneous characteristics of patients with PD who are often considered as one uniform group, without differentiating between cognitively intact patients and those with neuropsychological deficits or with hallucinations.

MRI IN PATIENTS WITH PD WITH COGNITIVE IMPAIRMENT AND HALLUCINATIONS

Cognitive impairment is common even in newly diagnosed patients with PD, occurring in 25 to 30% of cases.[1] Patients with cognitive deficits have an increased risk of developing dementia.[37,38] One study found that patients with PD with MCI diagnosis according to the criteria proposed by Petersen et al.[39] had gray matter reductions in temporal and frontal areas when compared with patients without MCI.[35] Another imaging study that identified MCI subtypes before conversion to various kinds of dementia found that the subtype most closely associated with conversion to dementia in PD was characterized by third ventricular enlargement and similar, though less severe, atrophy of the medial temporal lobe when compared with patients with MCI who converted to AD. Corrected hippocampal volumes in patients with MCI converting to AD were 0.084 mm^3 (left) and 0.078 mm^3 (right) when compared with values of 0.109 mm^3 (left) and 0.099 mm^3 (right) in patients with MCI converting to PD.[40] Unfortunately, MCI criteria for PD are not well defined and modified criteria used for AD[39] have mainly been used for the diagnosis. New criteria have recently been proposed for the diagnosis of dementia in PD,[41] and similar efforts should be made to create standardized criteria for MCI diagnosis in this condition.

Patients with visual hallucinations (VHs) present greater neuropsychological impairment in domains such as verbal memory, language, semantic fluency, and visuoperceptive functions than those without.[42–44] Longitudinal studies have pointed out the presence of VH as a predictor of dementia in PD.[45–47] We found that nondemented patients with PD with VH had gray matter loss in occipito-parietal regions when compared with patients without VH[34] and also presented hippocampal atrophy when compared with healthy controls.[48] These results suggest that pathological changes occurring in PD with VH are more marked and severe than those occurring in nonhallucinating patients with PD. As in AD,[7] hippocampal atrophy mainly affected the head of the structure and correlated with verbal memory.[48] Smaller hippocampal volumes and specifically the involvement of the hippocampal head have been identified as predictors of conversion to dementia in AD.[8] The same may apply to PD; in this initially nondemented sample of patients with PD with VH, nearly half met the criteria for dementia after 1 year follow-up.[49]

Manual ROI studies also provide evidence that specific cognitive deficits are related to specific structural changes in PD. Hippocampus volumes have been reported to correlate with memory scores[12–14,28,29] and overall cognitive performance scores,[12,13] but not with frontal functions.[50] In addition, amygdalar volumes have been reported to correlate with scores on these cognitive tests.[13,14] The atrophy of medial temporal structures probably runs in parallel and may underlie the memory dysfunctions associated with PD.

LONGITUDINAL MRI STUDIES IN PATIENTS WITH PD

The progression of regional brain atrophy with VBM in PD has only been investigated in two studies.[51,52] The first study showed limbic and temporo-occipital areas of gray matter reduction after a 25-month follow-up,[51] but the other study found no areas of gray matter loss in patients with PD after a follow-up period of 1.4 years.[52] The differences in these results may be explained by longer disease duration, increased age of patients, more prolonged follow-up, and use of uncorrected *P* values in the study in which atrophy was documented. In agreement with the first study, an earlier report by Hu et al.[53] found that annual brain volume loss was greater in patients with PD than in controls and these changes correlated with cognitive decline. However, other serial MRI studies using meas-

ures of global atrophy for monitoring disease progression reported no differences in atrophy rates between controls and nondemented patients with PD,[54,55] but found significantly increased atrophy in patients with PD with dementia when compared with nondemented patients with PD and controls.[54]

Longitudinal MRI studies should focus on tracking regional cortical changes in PD. Neuropathological studies in PD have proposed a six-stage system[56] of brain pathology to indicate a predictable sequence of ascending lesions that correlates with neurological deficits in the majority of patients with early onset and long duration of the disease, but this classification often fails to correlate with clinical severity and dementia in PD.[57] MRI studies permit assessment of morphological changes in vivo, allowing us to establish where morphological changes begin, and for which kind of patients these changes become more marked and which ones remain stable over time. Furthermore, if the areas that suffer the most atrophy over time are related to cognitive dysfunctions that lead to dementia, we would be able to determine objective markers for the development of dementia and provide evidence of therapeutic effect when modifying treatments related to the onset of dementia are available.

CONCLUSIONS

MRI studies have reported cortical atrophy in PD. ROI imaging studies have shown reduced hippocampal and amygdala volumes even in nondemented patients, and atrophy in these structures has been related to overall cognitive performance and memory deficits in PD. VBM studies have demonstrated that patients with PD with dementia present limbic and widespread neocortical gray matter loss, whereas patients with PD without dementia mainly present atrophy in frontal and temporal areas. Nondemented patients with PD with a higher risk of developing dementia, for example those with cognitive impairment and/or VHs, show greater atrophy than patients who do not present these risk factors. The involvement of the hippocampus in patients with PD with cognitive deficits has been identified in both ROI and VBM studies. Evidence of neocortical involvement is currently available only from whole brain VBM studies because to date no ROI studies have focused on the relationship between specific neocortical regions and cognitive domains. Overall, these findings suggest that cortical atrophy is related to cognitive dysfunction in PD and precedes the development of dementia. Cortical atrophy assessed by MRI may therefore be a useful early marker for the development of dementia in PD. The imaging findings reviewed here suggest that the term "subcortical dementia" is not adequate to describe the dementia occurring in PD. However, it should be borne in mind that the results from MRI structural studies in PD vary widely. The main problems are as follows: (1) the heterogeneity of samples studied; it is not always well defined whether the patients with PD included present cognitive deficits and/or psychiatric symptoms, and in fact the criteria used to diagnose dementia vary from study to study; (2) the inconsistency in applying correction for global cerebral volume in whole brain VBM and ROI studies; and (3) the inconsistency in the protocol used in VBM: optimized versus classical protocols, use of modulated versus unmodulated images, and the size of the Gaussian kernel in the smoothing.

To overcome these difficulties, we make the following recommendations: (1) cognitive and psychiatric symptoms in the sample should be defined using the criteria proposed by the Movement Disorder Task Force for the diagnosis of dementia in PD; (2) both raw and corrected volumes of the selected structures should be reported in ROI studies; (3) the standard guidelines[58] for reporting VBM studies should be followed, and a modulation of gray matter volume should be used based on the warping applied during normalization so as to minimize the danger of distortion. We also favor the use of the recently developed Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm, a nonlinear warping technique to minimize structural variation between subjects.[59]

Major challenges that remain in the field of MRI structural studies in PD are the need to establish patterns of atrophy that can predict different disease outcomes and to combine their use with other approaches, such as PET studies, using different tracers (FDG, MPPF, and FDDNP) to determine the etiopathogenesis of PD.

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