Hippocampal abnormalities and memory deficits in Parkinson disease

A multimodal imaging study

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ABSTRACT

Objectives: Investigating in a case-control study whether the performance scores of a group of patients with Parkinson disease (PD) without dementia on tests of declarative memory could be predicted by hippocampal volume reduction (as assessed by automatic segmentation of cerebral magnetic resonance [MR] images) or by the rate of microstructural alterations (as evaluated by diffusion tensor analysis of MR images).

Method: Twenty-five individuals with PD and 25 matched healthy control subjects underwent a 3-T MRI protocol with whole-brain T1-weighted and diffusion tensor imaging and a neuropsychological assessment. Images were processed to obtain indices of macrostructural (volume) and microstructural (mean diffusivity [MD]) variation of bilateral hippocampi. Neuropsychological evaluation included tests of verbal memory (15-minute delayed recall of a 15-word list) and visuospatial memory (20-minute delayed reproduction of Rey complex figure).

Results: MD in the hippocampi of patients with PD was significantly increased with respect to that of the group of control subjects. Moreover, patients with high hippocampal MD values obtained low memory scores. In contrast, no difference emerged between patients with PD and healthy control subjects for hippocampal size, and no relationship could be found between hippocampal volumes and memory scores.

Conclusions: These data confirm that the declarative memory impairment in patients with PD without dementia may be predicted by the rate of microstructural alterations in the hippocampal formation as detected by diffusion tensor imaging analysis. ***Neurology*® 2012;78:1939–1945**

GLOSSARY

ANCOVA = analysis of covariance; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **GM** = gray matter; **HC** = healthy control; **MD** = mean diffusivity; **MNI** = Montreal Neurological Institute; **PD** = Parkinson disease; **TE** = echo time; **TR** = repetition time.

An impairment of declarative memory is a frequent finding in patients with Parkinson disease (PD).[1] Attempts to correlate the memory deficit to reduced hippocampal volume in these patients have produced inconsistent data. Indeed, both postmortem studies[2,3] and in vivo brain investigations using MRI[4–9] reported mixed results.

Diffusion tensor imaging (DTI) measures the random motion of water in biologic tissues. Although DTI has been primarily used to investigate regional white matter changes, it is now clear that it can also be used to highlight microstructural alterations of gray matter,[10] particularly at the level of hippocampal formation.[11–14]

The present case-control study used a multimodal MRI approach, assessing volumetry and diffusivity at the same time, with the aim of investigating the presence of macrostuctural and microstructural changes at the level of the hippocampal formation in individuals with PD without dementia and its possible relationship with severity of the declarative memory impairment. Given the controversial evidence regarding volumetric changes in the hippocampi of patients with PD without dementia,[4–9] we made no predictions regarding the results of hip-

Supplemental data at www.neurology.org

Supplemental Data

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pocampal volumetric analysis in our PD sample. Instead, in view of previous evidence for healthy aged individuals[14] and for patients with mild cognitive impairment[10,13] and Alzheimer disease[11,12] that microstructural alterations of the hippocampal formation as detected by DTI are a better predictor of memory impairment than hippocampal volumetry, we made 2 main predictions regarding the results of the DTI analysis. First, we expected that participants with PD would show an increase in hippocampal diffusivity with respect to that in matched healthy individuals. Second, we expected an association in these individuals between increased hippocampal diffusivity and poorer performance on tests of declarative memory.

METHODS

Subjects. Sixty-two patients with idiopathic PD according to international guidelines[15] volunteered to participate in this study. Patients were recruited at the outpatient service for movement disorders of the Sant'Andrea Hospital, Department of Neurology, Sapienza University of Rome from March 2009 to March 2011 and were assessed at the Neuropsychiatry Laboratory of the I.R.C.C.S. Santa Lucia Foundation in Rome. Exclusion criteria for recruitment in the study were the following: 1) history of neurologic diseases other than idiopathic PD; 2) unclear history of dopaminergic treatment responsiveness; 3) presence of major medical illnesses; 4) known or suspected history of alcoholism, drug dependence and abuse, head trauma, or major psychiatric disorders according to the *DSM-IV-TR* criteria[16]; 5) presence of vascular brain lesions or marked cortical and subcortical atrophy based on visual inspection of all clinical MRI sequences by one trained neuroradiologist; 6) dementia diagnosis based on clinical examination or Mini-Mental State Examination[17]; and 7) insufficient vision and hearing to comply with the testing procedure. Of the 48 individuals who were considered eligible for participation in the study, 10 were excluded because of claustrophobia, 8 because of technical difficulties with the radiologic examination, and 5 because of evidence of focal parenchymal abnormalities. The resulting sample included 25 individuals (table 1). The patients with PD enrolled in the study had been receiving stable dopaminergic therapy for at least 2 months and did not require booster doses of L-dopa or dopamine agonists. We used the Unified Parkinson's Disease Rating Scale–Part III[18] for the clinical evaluation of motor symptoms. To ensure that there was a fixed interval for all patients between the first dose daily assumption and neuropsychological assessment, all testing and clinical evaluations were made 2 hours after the patients had received their first dose of medication.

Twenty-five healthy control (HC) subjects, rigorously matched with the patients with PD as for age, education, and gender, also participated in the study (table 1). These individuals were relatives of the patients with PD or elderly people attending community recreational centers. Exclusion criteria were the same as for patients with PD with the exception of points 1 and 2.

Neuropsychological and neuropsychiatric examination. Participants were given 2 declarative memory tests that evaluate retention of verbal and visuospatial material. In the 15-word list learning test,[19,20] the examiner reads 15 words (at a rate of 1 word per second) 5 times and immediately after each presentation the patient is asked to recall as many words as possible in any order. After a 15-minute interval, with interposed visuospatial tasks, the patient is asked to recall as many words as possible. Performance scores are represented by the number of words correctly recalled across the 5 immediate trials (maximum = 75) and the delayed trial (maximum = 15). In the Rey Figure Test,[21,22] the patient is required to make a freehand copy of a complex geometrical line drawing. After 20 minutes, with interposed verbal tasks, the patient is asked to reproduce the drawing. The performance score reflects accuracy of reproduction of any single element in the figure (maximum = 36). The neuropsychological battery also included tests that provide information about language (sentence construction[19]), executive functions (phonologic word fluency[19] and Stroop test interference time[23]) and constructional praxis (Copy of Rey Figure[21,22]). With the exception of the Stroop test (in which performance is expressed as time to complete), all other tests scores are expressed in terms of accuracy, and higher scores reflect better performance.

To investigate the neuropsychiatric symptoms of the patients with PD, we used the Neuropsychiatry Inventory.[24] In this scale, each item's score (ranging from 0 to 12) reflects both severity and frequency of behavioral symptoms, with 0 corresponding to the absence and 12 corresponding to its maximum frequency and severity.

MRI protocol and image processing. The imaging protocol included whole-brain T1-weighted and diffusion-weighted scanning using a 3-T Allegra MR imager (Siemens, Erlangen, Germany). Diffusion-weighted volumes were acquired using spin-echo echo-planar imaging (echo time [TE]/repetition time [TR] = 89/8,500 msec; bandwidth = 2,126 Hz/voxel; matrix size 128 × 128; 80 axial slices, voxel size 1.8 × 1.8 × 1.8 mm^3) with 30 isotropically distributed orientations for the diffusion-sensitizing gradients at a b value of 1,000 s/mm^2 and 6 b = 0

Table 1 Sociodemographic and clinical characteristics and hippocampal volumes and diffusivity of in the PD and HC groups and results of group comparisons[a]

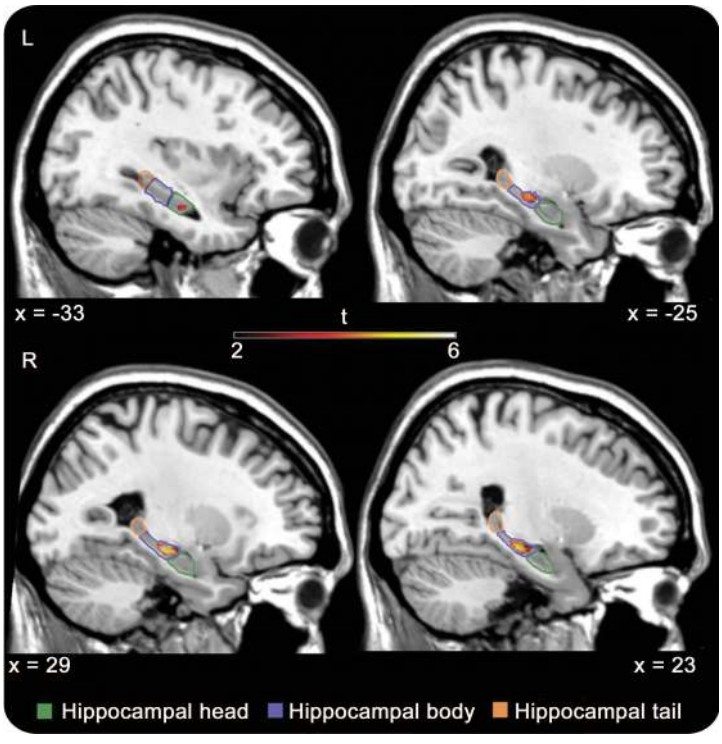
	PD	HC	*F*	*p* Value
Gender (F/M)	7/18	7/18		
Age, y, mean (S.D.)	65.0 (8.4)	65.0 (8.9)	0.0	1.00
Formal education, y, mean (S.D.)	12.6 (5.4)	12.3 (5.3)	0.1	0.86
MMSE score, mean (S.D.)	28.3 (1.2)	29.1 (1.8)	3.4	0.07
UPDRS score, mean (S.D.)	18.6 (8.7)			
Disease duration, y, mean (S.D.)	4.4 (4.0)			
Age at disease onset, y, mean (S.D.)	61.8 (8.9)			
Hippocampal volume, mean (S.D.)				
Right	3,375.2 (528.7)	3,293.7 (339.8)	0.2	0.70
Left	3,152.0 (589.3)	3,168.0 (398.7)	0.3	0.56
Hippocampal MD, mean (S.D.)				
Right	1,057.5 (101.3)	991.5 (70.4)	5.6	0.02
Left	1,036.4 (111.0)	992.8 (65.9)	2.1	0.16

Abbreviations: HC = healthy control; MD = mean diffusivity; MMSE= Mini-Mental State Examination; PD = Parkinson disease; UPDRS= Unified Parkinson's Disease Rating Scale.
[a] Group comparisons were made by analysis of variance for demographic and clinical measures and by analysis of covariance on rank transformations of original data with age as a covariate for anatomical measures.

images. Scanning was repeated 3 times to increase the signal/noise ratio. T1-weighted images were obtained using a modified driven equilibrium Fourier transform sequence (TE/TR = 2.4/7.92 msec; flip angle 15°; voxel size 1 × 1 × 1 mm^3). T1-weighted and DTI images were submitted to several processing steps. First, to explore (on a voxel-by-voxel basis) the differences between HCs and patients with PD in gray matter (GM) volume and the correlation between GM volume and scores in cognitive testing, T1-weighted images were processed for the analysis using an extension of statistical parametric mapping 5 (SPM5; Wellcome Department of Imaging Neuroscience, London, UK), specifically, the VBM5.1 toolbox (http://dbm.neuro.uni-jena.de/vbm) running in MATLAB 2007b (MathWorks, Natick, MA). Images were bias field corrected, tissue classified, and registered using linear (12-parameter affine) and nonlinear transformations (warping) within the same generative model. Subsequently, GM segments were multiplied by the nonlinear components derived from the normalization matrix to preserve actual GM values locally (modulated GM volumes). Finally, the modulated GM volumes were smoothed with a Gaussian kernel of 8-mm full-width at half-maximum to obtain modulated, normalized, and smoothed GM images on which all analyses were performed.

Second, in order to extract volume and mean diffusivity (MD) of the hippocampus, diffusion tensor and T1-weighted images were processed using the FSL 4.1 package (http://www.fmrib.ox.ac.uk/fsl/). In brief, after eddy current and head motion distortion correction, DTI data were averaged and concatenated into 31 (1 b 0 + 30 b 1,000) volumes. A diffusion tensor model was fitted at each voxel to generate fractional anisotropy (FA) and MD maps. To register DTI data to the T1-weighted anatomic images, we calculated a full affine transformation between FA maps and brain-extracted whole-brain volumes from T1-weighted images.[25] The calculated transformation matrix was then applied to the MD maps with identical resampling options. Then, anatomic T1-weighted images were processed with the tool FIRST 1.1 (integrated in FSL) to segment right and left hippocampi, which were then used as 1) binary masks for which mean values of volume and MD were calculated for each individual and 2) inclusive regions of interest for performing voxel-by-voxel analyses of GM volume and MD.

Figure 1 **Increase in hippocampal diffusivity in patients with Parkinson disease compared with healthy control subjects**



Statistical results are superimposed over the standard Montreal Neurological Institute template (x coordinates are reported). Hippocampal head, body, and tail (approximately derived with reference to segmentations reported in Malykhin et al. 2007)[36] are highlighted in green, blue, and orange, respectively.

Standard protocol approvals, registrations, and patient consents. The Joint Ethics Committee of the Fondazione Santa Lucia approved the experimental protocol. All patients gave written informed consent for participation in the study.

Statistical analyses. Data distribution for some anatomic measures (right hippocampal volume and left hippocampal MD) violated the parametric test assumption of homogeneity of variance between groups ($p < 0.05$). For this reason and to control for possible age effects, we first performed rank transformation of anatomic data and then compared groups by means of parametric analysis of covariance (ANCOVA) with age as a covariate. For the neuropsychological and clinical measures, which fitted the parametric test assumption of homogeneity of variance between groups, the parametric analyses of variance and ANCOVAs (with age or MD as covariates) were performed on original data. Nonparametric correlation coefficients (Spearman rho) were applied to determine whether anatomic and neuropsychological data were significantly associated. To control for possible age effects on anatomic measures, native data of hippocampal volumes and MD were first corrected for age according to the results of regression analyses.

Hippocampal voxel-by-voxel analyses of GM volume and MD were performed within the framework of the general linear model using SPM5. Specifically, we ran 1) two 2-sample *t* tests to highlight differences in GM volume and MD between HCs and patients with PD and 2) several multiple regression models to show significant correlations between hippocampal GM volume and MD (used as dependent variables) and neuropsychological testing scores (used as regressors). To avoid type I errors (i.e., accepting false-positive results), these analyses were performed using the random fields theory family-wise error correction ($p < 0.05$ corrected for multiple comparisons), which controls for any false-positive results across the entire volume.

RESULTS

MD is increased in the hippocampus of patients with PD. Average hippocampal volumes and MD in the PD and HC groups are reported in table 1 (see also figures e-1 through e-7 on the *Neurology*® Web site at www.neurology.org). No group difference was detected for volume, but participants with PD had on average higher hippocampal MD values than HCs; the difference was significant on the right side.

Results of the voxel-by-voxel analyses (figure 1) confirmed these results. Although no differences were observed in GM hippocampal volume, patients with PD showed a significant increase of MD in several bilateral hippocampal regions, located approximately in the body of both hippocampi (Montreal

Table 2 Performance scores of participants in the PD and HC groups on the tests of the neuropsychological battery and Neuropsychiatric Inventory and results of ANOVAs comparing the 2 groups

	PD	HCs	$F_{1,48}$	*p* Value
Phonologic word fluency, mean (S.D.)	29.8 (11.8)	35.2 (11.3)	2.75	0.10
Sentence construction, mean (S.D.)	17.1 (6.3)	20.8 (5.6)	4.87	0.03
Rey Figure Copy, mean (S.D.)	29.2 (4.6)	31.7 (3.6)	4.57	0.04
15-Word list, mean (S.D.)				
Immediate recall	38.2 (10.3)	43.6 (7.8)	4.37	0.04
Delayed recall	8.2 (3.3)	9.4 (2.4)	2.05	0.16
Rey's Figure memory reproduction, mean (S.D.)	15.2 (6.6)	17.1 (6.1)	1.20	0.28
Stroop, mean (S.D.)				
Color time, s	22.5 (6.4)	22.9 (6.1)	0.05	0.82
Word time, s	17.3 (6.2)	17.1 (5.6)	0.01	0.90
Interference time, s	41.3 (13.5)	46.2 (14.4)	1.53	0.22
NPI, mean (S.D.)[a]				
Delusions	0.0 (0)			
Hallucinations	0.4 (1.8)			
Agitation	0.0 (0.0)			
Depression	2.6 (2.6)			
Anxiety	3.0 (2.8)			
Euphoria	0.0 (0.0)			
Apathy	1.2 (1.9)			
Disinhibition	0.4 (1.8)			
Irritability	1.2 (2.0)			
Aberrant Motor Behavior	0.0 (0.0)			
Nighttime Behavioral Disturbances	3.8 (4.2)			
Appetite/Eating Disturbances	0.2 (1.2)			
Total score	12.9 (9.6)			

Abbreviations: ANOVA = analysis of variance; HC = healthy control; NPI = Neuropsychiatric Inventory; PD = Parkinson disease.
[a] The NPI was administered only to patients with PD.

Neurological Institute [MNI] coordinates: −24, −22, −12 [left] and 26, −22, −10 [right]) and extending to the head of the left ones (MNI coordinates: −34, −12, −20).

Patients with PD performed worse than HCs on memory tests. As reported in table 2, patients with PD scored significantly worse than HCs on the immediate recall of the 15-word list. HCs also performed better than patients with PD on the delayed recall of the word list and the memory reproduction of the Rey Figure Test, but in these cases, the differences fell short of significance. Patients with PD scored significantly worse than HCs also in sentence construction and Rey Figure Copy.

Increased hippocampal MD is associated with reduced memory performances in patients with PD. As reported in table 3, hippocampal volumes were not correlated with memory scores in either the PD or the HC group. In the HC group, individuals with high MD values in the left hippocampus obtained low scores on the immediate and delayed recall of the word list. In the PD group, patients with high MD values in the right hippocampus obtained low scores on all memory tests, and patients with high MD values in the left hippocampus obtained low scores on the delayed recall of the word list. Although correlation coefficients between hippocampal MD values and memory scores were consistently higher in the PD than in the HC group, in no case did this difference approached the level of statistical significance ($p > 0.10$).

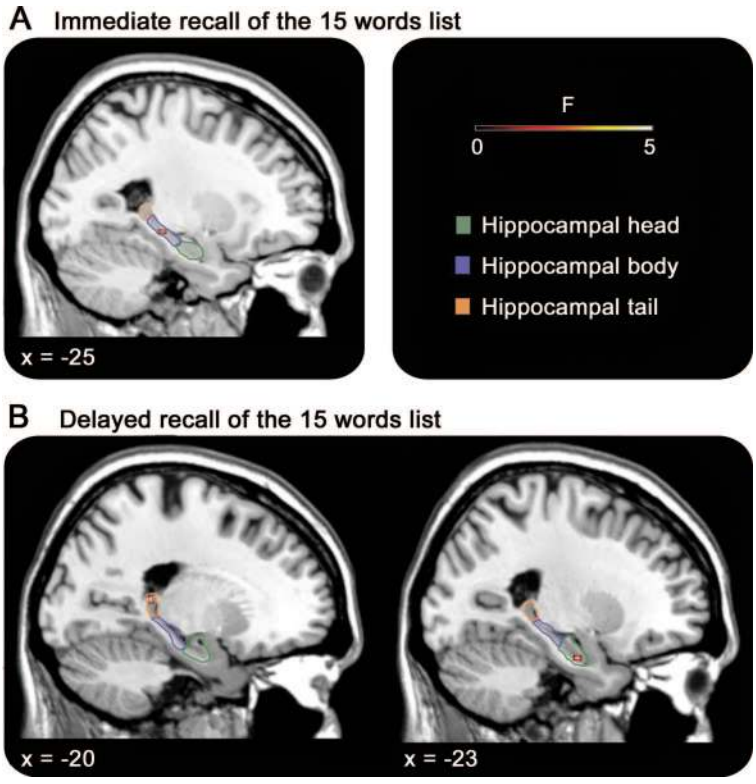
Results of the voxel-by-voxel analyses (figure 2) partially confirmed the region of interest−based results. No significant correlations were found between GM hippocampal volume and memory scores in either the PD or the HC group. As for hippocampal MD, no significant correlations were found in the HC group. Conversely, in the PD group, patients with high MD values in the left hippocampus obtained low scores on both immediate and delayed recall of the word list. The areas of significant correlation were located approximately in the body of the hippocampus for immediate recall and in the head and tail for delayed recall. Because MD variations

Table 3 Spearman rho coefficients between anatomical measures and memory scores in the HC and PD groups

	HC			PD		
	15-Word list immediate recall	15-Word list delayed recall	Rey Figure reproduction	15-Word list immediate recall	15-Word list delayed recall	Rey Figure reproduction
Hippocampal volume						
Right	0.26	0.22	0.16	0.15	0.25	0.26
Left	−0.07	−0.06	0.24	0.13	0.21	0.05
Hippocampal MD						
Right	−0.05	0.02	0.18	−0.33[a]	−0.36[a]	−0.43[a]
Left	−0.36*	−0.33*	0.10	−0.20	−0.34[a]	−0.28

Abbreviations: HC = healthy control; PD = Parkinson disease.
[a] $p < 0.05$.

Figure 2 Correlation between scores of immediate (A) and delayed (B) recall of the 15-word list and left hippocampal mean diffusivity in patients with Parkinson disease



Statistical results are superimposed over the standard Montreal Neurological Institute template (x coordinates are reported). Hippocampal head, body, and tail (approximately derived with reference to segmentations reported in Malykhin et al., 2007)[36] are highlighted in green, blue, and orange, respectively.

can be influenced by age, analyses were rerun in areas of significant relationship including age as covariate. Results did not change. Moreover, when the analyses were limited to the hippocampal regions in which a significant MD difference emerged between patients with PD and HCs, a significant correlation between MD and immediate recall of the word list was found in the body of the left hippocampus (MNI coordinates: −26, −20, −20).

The predictability of increased hippocampal MD over the reduced memory performance in patients with PD was confirmed by ANCOVA. Indeed, the between-group difference in the 15-word list immediate recall was no longer significant after covarying for the average MD of the left and right hippocampus ($F_{1,48} = 2.07$; $p > 0.15$).

DISCUSSION Our data did not confirm the hypothesis that macrostructural changes in the hippocampi of patients with PD without dementia, as reflected by reduced size of the anatomic formation, is related to poor declarative memory. Indeed, hippocampal volumes in patients with PD were neither reduced in comparison with those of HCs nor significantly associated with their performance on memory tests. This negative finding, which was confirmed both in the analysis of overall hippocampal volumes and in the voxel-by-voxel analysis of regional GM volume, was expected because of previous evidence of hippocampal volumes that were not different in patients with PD without dementia and HCs[8,9] and a nonsignificant association between hippocampal size and memory scores in patients with PD.[4,9] However, other studies reported either a significant volumetric reduction of the hippocampi[4–7] or a significant relationship between hippocampal size and memory performance.[5,7] The reasons for these inconsistent results are unclear. It could be that discrepancies in the exclusion/inclusion criteria adopted in the different studies and differences in disease duration or other clinical variables negatively influenced the possibility of observing an effect of hippocampal volume on memory performance in patients with PD.

Conversely, our data are consistent with the hypothesis that microstructural alterations in the hippocampi of patients with PD without dementia, as detected by DTI analysis, are associated with a decrement in their declarative memory performance. First, we found that MD in the hippocampus of patients with PD was bilaterally increased with respect to that of the individuals in the HC group. In fact, when the average MD of the hippocampi was considered, the between-group difference was statistically significant only on the right side. However, the voxel-by-voxel analysis revealed areas of significant MD increase in both the right and left hippocampi of patients with PD. Second, patients with PD scored worse than HCs on tests of declarative memory for both verbal and visuospatial material, the group difference reaching the conventional level of statistical significance on the test of immediate recall of a word list. Finally, the correlational analysis documented that in the PD group individuals with high values of MD in the right hippocampus scored poorly on both verbal and visual memory tests, and patients with high MD values in the left hippocampus performed poorly on the verbal memory tests. The VBM analysis confirmed a significant association in the PD group between increased MD in some areas of the left hippocampus and reduced verbal memory performance. As further confirmation of the role exerted by increased MD in the hippocampal formation on reduced memory performance in the PD group, after covarying for the average hippocampal MD, the between-group difference in the immediate recall of the word list was no longer significant.

Although the precise neural correlates of altered diffusivity in GM structures are not completely known, it is generally believed that, in pathologic

states, an increase of diffusivity is an expression of an enlargement in the extracellular space due to altered cytoarchitecture, suggesting immaturity or degeneration.[26,27] In deep GM assemblies, this might reflect either direct pathologic damage or secondary degeneration due to disruption of white matter tracts linking them to other structures, possibly leading to cortical dysfunctions.[28] In physiologic states, extracellular water diffusion is influenced by different factors such as the size of the pores between the cells and the cellular structure, density, and surface.[29] The changes in extracellular space diffusion parameters can affect the efficacy of synaptic as well as extrasynaptic transmission.[30] Along this line of evidence, GM mean diffusivity has been extensively linked to cognitive performance.[14,30–32]Because neuropathologic studies of the hippocampal formation in patients with PD showed normal cell counts but a significant increase in Lewy bodies and Lewy neuritis mainly in the CA2 and CA3 sectors,[33,34] we may speculate that increased water diffusivity in the hippocampal formation of patients with PD, as documented by DTI analysis of magnetic resonance images, reflects the rate of α-synuclein deposition (perhaps mediated by reduced synapse or spine density).

The main limitation of the present study is represented by the relatively small sample size, which suggests caution in the generalizability of study results. A possible source of confound is represented by the fact that all participating patients with PD were examined while they were receiving chronic L-dopa therapy. In light of the reported adverse effect of L-dopa on mesial temporal lobe–mediated memory functions,[35] it would be interesting to evaluate whether the same pattern of results is observed in untreated patients.

The evidence that microstructural alterations in the hippocampus of patients with PD without dementia are related to a decrement in declarative memory functioning may be clinically relevant. Indeed, initial memory loss associated with increased hippocampal MD could represent the prodromal signal of oncoming dementia. Further follow-up studies are needed to confirm the prognostic value of concomitant brain MRI-DTI and neuropsychological assessment in the early detection of cognitive deterioration in patients with PD.

AUTHOR CONTRIBUTIONS

Dr. Carlesimo: study concept and design; analysis and interpretation of data; statistical analysis; drafting the manuscript for content, including medical writing for content. Dr. Piras: analysis and interpretation of data. F. Assogna: analysis and interpretation of data. Dr. Pontieri: study concept and design. Dr. Caltagirone: study concept and design. Dr. Spalletta: study concept and design; analysis and interpretation of data; statistical analysis; revising the manuscript for content, including medical writing for content.

DISCLOSURE

Prof. Carlesimo, Dr. Piras, Dr. Assogna, Prof. Pontieri and Prof. Caltagirone report no disclosures relevant to the manuscript. Dr. Spalletta received honoraria from serving as a consultant for Novartis and received funding for expenses for participating in a scientific congress from Servier. **Go to Neurology.org for full disclosures.**

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Thank you, Dr. John F. Kurtzke!

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- June 1968; 18 (6 Part 2):1–10
- May 1970; 20 (5 Part 2):1–59
- February 1988; 38 (2):309–316

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