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DTI Correlates of Distinct Cognitive Impairments in Parkinson's Disease

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Abstract: The spectrum of cognitive symptoms in Parkinson's disease (PD) can span various domains, including executive function, language, attention, memory, and visuospatial skills. These symptoms may be attributable to the degradation of projection fibers associated with the underlying neurodegenerative process. The primary purpose of this study is to find microstructural correlates of impairments across these cognitive domains in PD using diffusion tensor imaging (DTI). Sixteen patients with PD with comprehensive neuropsychological evaluation and DTI data were retrospectively studied. Fractional anisotropy (FA) and mean diffusivity (MD) were assessed using regions-of-interest (ROI) analysis and confirmed with a voxel-based approach. Executive function directly correlated with FA and inversely correlated with MD in mostly frontal white matter tracts, especially the anterior limb of the internal capsule and genu of the corpus callosum. Likewise, language and attentional performance demonstrated correlations with DTI parameters in the frontal regions, but the attention domain additionally recruited regions widespread throughout the brain, with the most significant correlation identified in cingulate gyrus (cingulum). Lastly, memory impairment mainly involved MD alterations within the fornix. No significant correlations were found between visuospatial skills and DTI measures. Despite some overlap, unique patterns of white matter diffusivity underlie impairments in distinct cognitive domains in patients with PD. DTI combined with neurocognitive tests may be a valuable biomarker for identifying cognitive impairments in PD. *Hum Brain Mapp 35:1325–1333, 2014.*

Key words: cognition; Parkinson's; connectivity; tractography; neurodegenerative; white matter; neuroimaging; brain

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INTRODUCTION

The cognitive impairments of Parkinson's disease (PD) can affect multiple domains, including frontal/executive function, memory, visuospatial skills, attention, and language [McKinlay et al., 2009; Zgaljardic et al., 2003]. Despite its prevalence and impact, the spectrum of impairment and neural basis of cognitive impairments in PD are not fully characterized. Patterns of cognitive impairments are likewise variable, including patients with predominant impairments in fronto-striatally mediated function, others with impairments of temporal lobe-mediated functions, and others with both [Foltynie et al., 2004a; Williams-Gray et al., 2007, 2009]. The heterogeneity is likely attributable to distinct patterns and combinations of neurochemical degeneration (e.g., dopaminergic nigrostriatal degeneration vs. cholinergic degeneration (e.g., basal nucleus of Meynert [Gaspar and Gray, 1984])) and unique anatomic patterns of Lewy body deposition (in contrast to the uniform progression of synucleinopathies suggested by Braak et al. [2003]. While frontal executive impairments are likely dopaminergically mediated, varying with a common functional polymorphism in the catechol-*O*-methyltransferase gene (COMT $Val^{158}Met$) which modulates prefrontal dopamine availability [Foltynie et al., 2004b; Williams-Gray et al., 2009], temporal lobe mediated impairments are more likely related to cholinergic impairments and more extensive subcortical and neocortical Lewy body deposition [Emre, 2003; Gaspar and Gray, 1984; Goris et al., 2007; Mattila et al., 2000; Williams-Gray et al., 2009]. Demonstration of the anatomic basis and separability of these distinct patterns of cognitive impairment would greatly enhance our understanding of these processes, facilitate anatomically driven investigations of the neurobiological processes underlying these impairments, and impact the clinical management of patients with PD.

Several studies have confirmed the relationship between white matter changes and the motor manifestations of PD [Bohnen and Albin, 2011; Yoshikawa et al., 2004; Zhan et al., 2012]. Likewise, we hypothesize that the cognitive aspects of the disease are also likely due to neurodegenerative processes disrupting the integrity of white matter microstructure but within distinct cerebral networks. However, the neuroanatomical basis and topography of the neurobiological processes that account for these cognitive impairments have not been well characterized due to limitations in prior neuroimaging analyses and the use of coarse, incomplete, and inadequate neurocognitive assessments, like the mini-mental status examination (MMSE) in Parkinson's patients [Gattellaro et al., 2009; Hattori et al., 2012]. Studies have shown that tools that are not specific for PD (e.g., MMSE and SF-36) have poor accuracy and reliability in diagnosing cognitive impairment, dementia, and quality-of-life (QOL) in PD [Brown et al., 2009; Kulisevsky and Pagonabarraga, 2009].

DTI parameters, such as fractional anisotropy (FA) and mean diffusivity (MD), can be used to infer neural substrates underlying specific cognitive functions when correlated with neuropsychological performance [Sasson et al., 2012]. In this study, we used DTI to evaluate the relationship between measures of white matter integrity in predefined regions-of-interest (ROIs) and performance in five distinct cognitive domains (executive function, language, attention, memory, and visuospatial skills) in 16 patients with PD with varying degrees of cognitive impairment, as detailed using comprehensive neuropsychological testing. A *post hoc* voxel-based analysis was supplemented to confirm the ROI-based results. We tested two hypotheses: (1) Impairments in different cognitive domains are associated with changes in white matter integrity in distinct cerebral networks. (2) The degree of impairment in each domain correlates with quantitative measures of white matter integrity within the distinct networks.

METHODS

Subjects

Sixteen patients (11 males, 5 females, average age 62.2 ± 9.6 years) who had undergone evaluation for stereotactic implantation of deep brain stimulators for PD were included in this retrospective study. All patients were from UCLA's stereotactic neurosurgery database through August 2011 and had detailed preoperative neuropsychological testing results and MRI data. Patients' Hoehn and Yahr clinical staging while on medication had a mean of 2.3 ± 0.9 with mean disease duration of 9.5 ± 6.0 years. All studies and analysis were done after obtaining approval from and in accordance with guidelines provided by the UCLA Institutional Review Board.

Neuropsychological Measures

Neuropsychological testing was performed as part of evaluation for deep brain stimulation surgery in a clinical context. All assessments were done in an "on" medication condition and included comprehensive testing spanning five cognitive domains (executive function, memory [short-term and long-term], visuospatial skills, language, and attention). Due to the inhomogeneity of the neurocognitive tests used to evaluate each domain in this clinical dataset and in order to reduce the feature set analyzed, we derived a single score for each patient in each cognitive domain based on a pre-selected list of domain-representative tests. Each patient's detailed neuropsychological testing result was carefully and independently reviewed by two independent evaluators, who calculated an average percentile score for each domain for each subject using the age-matched percentile scores from the domain-representative tests. Age-matched percentile scores rather than raw performance scores were used to correct for potential age-related differences in performance. In cases with more than a 5 percentile discrepancy, a third evaluator provided

TABLE 1. Results of neuropsychological evaluation for each cognitive domain

	Percentile Score		
	Mean	SD	Range
Executive function	44.16	22.57	7–82
Color-word interference			
Letter fluency			
Category fluency			
Category switching			
Number-letter switching			
Short-term memory	39.48	26.16	1–83
WMS-IV logical memory I			
CVLT Trials 1–5			
Short delay free recall			
Long-term memory	44.44	26.93	2–79.5
WMS-IV logical memory II			
Long delay free recall			
Visuospatial skills	43.47	29.32	6–91
NAB visual discrimination			
Hooper VOT			
WAIS matrix reasoning			
Block design			
Language	48.56	28.94	6–95
WAIS verbal comprehension			
Boston naming test			
Letter fluency			
Animal fluency			
WAIS vocabulary			
Attention	40.48	26.48	2–91
Trails A			
Stroop/DKEFS-word			
Stroop/DKEFS-color			
WAIS digit span			

Lower percentile scores indicate more impairment. WMS-IV = Wechsler Memory Scale, Fourth Edition; CVLT = California Verbal Learning Test; NAB = Neuropsychological Assessment Battery; VOT = Visual Organization Test; WAIS = Wechsler Adult Intelligence Scale; DKEFS = Delis Kaplan Executive Function System. SD = standard deviation.

a blind evaluation and determined the most representative score for the domain in question (Table I).

Image Acquisition

MRI data were acquired with a 3.0 Tesla scanner. Sequences included a high-resolution T1-weighted anatomical scan with the following parameters: Repetition time (TR) = 11 ms, Echo time (TE) = 2.81 ms, flip angle = 20°, matrix size = 256 × 256, slice thickness = 0.90 mm with no gap, and resolution = 0.94 × 0.94 × 0.90 mm^3. In addition, all patients had undergone a 20-direction DTI acquisition, except for one with a 60-direction acquisition, using diffusion weighted single-shot spin-echo EPI with b = 1,000 s/mm^2, TR = 9,100 ms–14,400 ms, TE = 87 ms, matrix size =128 × 128, slice thickness = 2 mm with no gap, resolution = 2 × 2 × 2 mm^3. In each subject, at least one volume was acquired without the use of a diffusion gradient (b = 0 s/mm^2).

Data Analysis

Imaging analysis was carried out using FSL tools (http://www.fmrib.ox.ac.uk/fsl). The first preprocessing step was to manually inspect each DTI data to eliminate any volumes with large distortions that could potentially skew the data. Next, skull stripping with the brain extraction tool (BET) was applied to both the T1 and b = 0 image in each subject. Eddy current correction was used to correct for distortions and head motion on the DTI sequences by aligning the diffusion weighted images to the b = 0 image. Tensors were determined using DTIFIT, producing FA and MD maps.

For the ROI-based analysis, 40 ROIs (Table II), from Johns Hopkins University's Mori white matter atlas (http:// cmrm.med.jhmi.edu), were transformed into each patient's diffusion space using transformation matrices created from nonlinear registration between the patient's diffusion space and standard space (FMRIB58_FA). Using fslstats, average FA and MD values were calculated for each ROI and were linearly regressed against neurocognitive scores in each domain. Only correlations that exceeded a statistical threshold of $P < 0.01$ are reported.

A *post hoc* regionally unbiased voxel-based analysis was carried out to account for multiple comparisons and verify the significant results from the ROI analysis. Nonlinear registration was applied to align all subjects' 3D FA images to the FMRIB58_FA template and then all FA

TABLE 2. Mori atlas white matter ROIs

Genu	Genu of corpus callosum
Body	Body of corpus callosum
Splenium	Splenium of corpus callosum
Fornix	Fornix (column and body)
CST	B. Corticospinal tract
CP	B. Cerebral peduncle
ALIC	B. Anterior limb of internal capsule
PLIC	B. Posterior limb of internal capsule
RLIC	B. Retrolenticular limb of internal capsule
ACR	B. Anterior corona radiata
SCR	B. Superior corona radiata
PCR	B. Posterior corona radiata
PTR	B. Posterior thalamic radiation (include optic radiation)
SS	B. Sagittal stratum (include ILF and IFO)
EC	B. External capsule
CG	B. Cingulate gyrus (Cingulum)
HC	B. Hippocampus (Cingulum)
FST	B. Fornix stria terminalis
SLF	B. Superior longitudinal fasciculcus
SFO	B. Superior fronto-occipital fasciculus
IFO	B. Inferior fronto-occipital fasciculus
TAP	B. Tapetum

B = bilateral; ILF = inferior longitudinal fasciculus

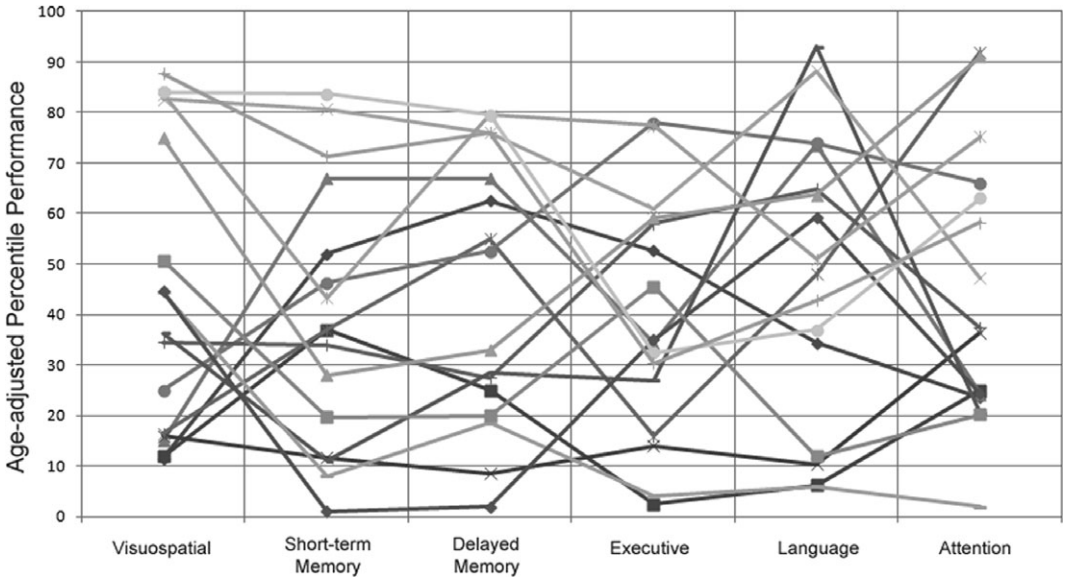

Figure 1.

Variability in cognitive domain performance for each individual. Performance across domains was variable across subjects, with individual subjects demonstrating particular strengths and weakness in distinct domains.

TABLE 3. Significant ROI-based correlations of FA and MD with cognitive domains verified with voxelwise analysis

	Fractional anisotropy		Mean diffusivity	
cognitive domains	ROIs	*P-value*	ROIs	*P*-value
Executive function	Anterior corona radiata, right	0.0087	Anterior corona radiata, right[1]	0.0023
	Anterior limb of internal capsule, left	0.0029	Anterior corona radiata, left[1]	0.0063
	Genu	0.0099	Anterior limb of internal capsule, left	0.003
	Posterior thalamic radiation, right[1]	0.0044	Genu	0.0097
			Posterior corona radiata, left[1]	0.0092
			Sagittal stratum, left[1]	0.0041
			Superior fronto-occipital fasciculus, left[1]	0.0037
Short-term memory	None		Fornix	0.0037
Long-term memory	None		Anterior corona radiate, right[1]	0.0068
Visuospatial	None		None	
Language	Anterior limb of internal capsule, left	0.0087	Anterior corona radiata, right	0.0074
	Sagittal stratum, right	0.0015	Anterior corona radiata, left	0.0068
			Sagittal stratum, right	0.0031
			Sagittal stratum, left[1]	0.0035
			Superior fronto-occipital fasciculus, left	0.0077
Attention	Cingulate gyrus, right	0.0071	Anterior corona radiata, right	0.0013
	Cingulate gyrus, left	0.0003	Anterior limb of internal capsule, left	0.0046
	Posterior thalamic radiation, right	0.0056	Corticospinal tract, left	0.007
	Posterior thalamic radiation, left	0.001	Cingulate gyrus, left	0.0006
	Retrolenticular part of internal capsule, left	0.0096	Hippocampus, left	0.0031
	Sagittal stratum, left	0.0079	Posterior corona radiata, right	0.0062
	Superior fronto-occipital fasciculus, right	0.004	Posterior corona radiata, left	0.0081
	Superior fronto-occipital fasciculus, left	0.0046	Posterior thalamic radiation, left	0.0027
			Retrolenticular part of internal capsule, left	0.0017
			Sagittal stratum, left	0.0087
			Splenium	0.001
			Superior corona radiata, right	0.0066
			Superior corona radiata, left	0.0064
			Superior fronto-occipital fasciculus, right	0.0049
			Superior fronto-occipital fasciculus, left	0.0013

Significant findings from the ROI analysis are listed with P values, $P < 0.01$. Verifications of the ROI results with *post hoc* voxelwise analysis are significant ($P < 0.05$) except when indicated by a superscript 1.

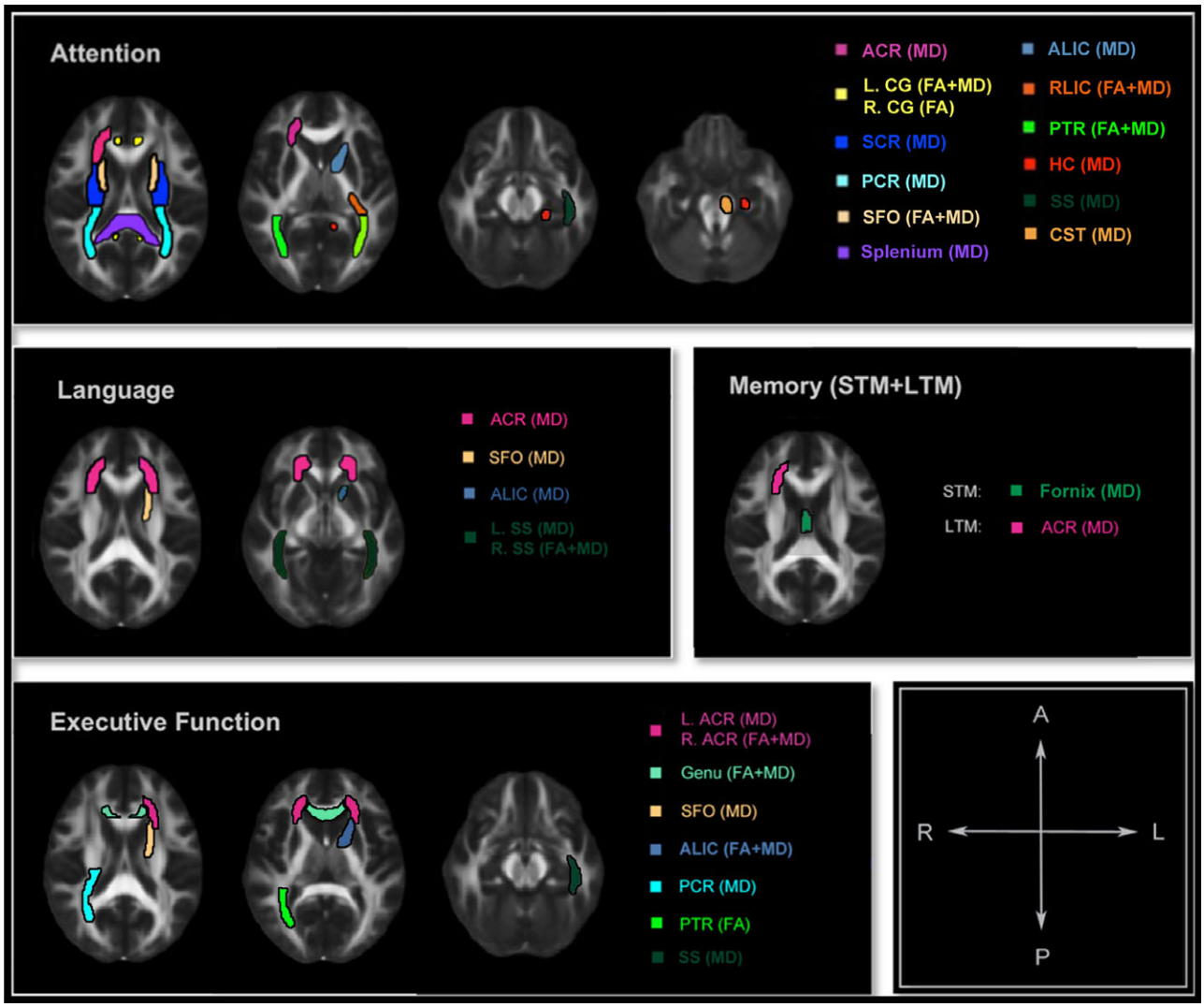

Figure 2.
Statistically significant ROIs in each cognitive domain overlaid on top of a standard brain in axial view. Refer to Table III for abbreviated ROIs. L = left; R = right; A = anterior; P = posterior.

images were merged to create a single 4D FA image. Using the transformations from the FA normalization, each subject's MD image was similarly registered to the standard target and a merged 4D MD image was generated. A 2 mm full width at half maximum (FWHM) Gaussian smoothing was applied to the normalized FA and MD images. Voxelwise statistics was run to test for correlations between the FA and MD images with each cognitive domain performance using nonparametric permutation t tests (3,000 permutations) and threshold-free cluster enhancement (TFCE). The significance threshold was set at $P < 0.05$.

Additional analyses were performed to evaluate for possible confounding variables, particularly age. Cognitive performance in each domain was also evaluated for correlation with disease severity measures including Hoehn and Yahr, disease duration, total UPDRS (off state), and UPDRS III motor performance (off state) in patients in whom such data was available ($n = 7$).

RESULTS

Mean age-matched percentile performance scores in each cognitive domain are reported in Table I, ranging between 39.48 and 48.56. No significant differences were noted between performance across domains (one-way ANOVA, $P < 0.05$), but individual patient performance varied across domains, as shown by the large range, with some patients having borderline performance (less than 10th percentile) in one domain while performing

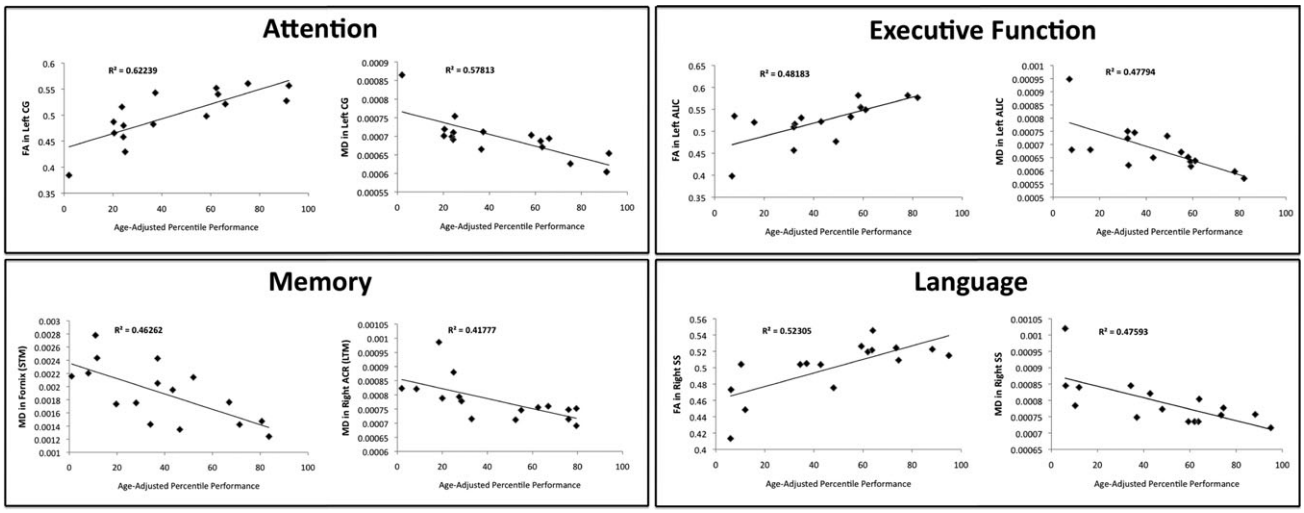

Figure 3.

Regression analyses between DTI indices and measures of cognitive performance. Representative regions of the most significant correlations from each domain are graphed. FA positively correlated with neurocognitive scores, whereas, MD negatively correlated with the scores.

superiorly in other domains (greater than 90th percentile) (Fig. 1). There were no significant correlations between age and either neurocognitive scores in each domain or FA and MD values in the 40 ROI evaluated (85 comparisons), with the exception of MD values within the right hippocampus and age ($P = 0.0083$). No significant correlations were observed between neurocognitive scores and disease severity measures.

Significant ROI correlations ($P < 0.01$) between the neurocognitive domain scores and DTI parameters were identified in every cognitive domain except for the visuospatial domain (Table III). A graphical representation of the significant interactions is presented in Figures 2 and 3. In general, FA results positively correlated with improved performance in each domain, whereas MD showed negative correlations with domain-specific scores (Fig. 3). Overall, MD values were more often correlated with scores in each domain than FA values (Table III). The results were not significantly lateralized. The most representative results are summarized here briefly. Executive function primarily correlated with frontal connecting tracts including the left anterior limb of the internal capsule (ALIC) and genu of the corpus callosum (genu). Linguistic performance was mostly correlated with the left ALIC, left superior-fronto-occipital fasciculus (SFO), and bilateral sagittal strata (SS). The attention domain had the most associations identified throughout the brain with strong correlations in the splenium of corpus callosum (splenium), the left sides of cingulate gyrus (CG), posterior thalamic radiation (PTR), retrolenticular limb of the internal capsule (RLIC), and SS. The *post hoc* voxel-based analysis (accounting for multiple comparisons) verified the findings of the ROI-based approach with few exceptions (detailed in Table III).

DISCUSSION

Although a number of DTI studies have been conducted to better understand PD pathology, only a few have focused on the cognitive correlates of the disease and mostly relied on the use of MMSE as a cognitive assessment instrument [Hattori et al., 2012], our study is the first to demonstrate a comprehensive approach to studying the broad range of cognitive deficits in PD by using DTI coupled with domain specific neurocognitive tests. In our study, we found that unique patterns of white matter signal characteristics (i.e., FA and MD values derived from DTI) are related to differential performance in distinct cognitive domains in patients with PD. While previously recognized in the neuropsychological literature [Kantarci et al., 2011; Sasson et al., 2012], this study confirms that, despite some overlap, impairments in distinct cognitive domains are subserved by different white matter networks. Moreover, the degree of impairment in each domain is related to the degree to which the white matter region of interest is affected (Fig. 3).

Spectrum of Neurocognitive Impairments in PD

The spectrum of cognitive impairments observed in this population confirms previous reports that have shown PD to involve cognitive deficits across multiple domains, including frontal/executive function, language, attention, memory, and visuospatial skills [Karlsen et al., 1998; Schrag et al., 2000]. Previous reports have revealed that most patients with PD exhibit an attentional-executive dysfunction with possible progression to impairments in language, memory, and visuospatial performance [Janvin et al., 2003; Muslimovic et al., 2005]. Cognitive

impairments related to impairments in frontal lobe function appear to be the most prominent and typically occur early in the disease stage [Bruck et al., 2004; Farina et al., 2000; Lees and Smith, 1983; Taylor et al., 1986]. However, the nature of cognitive impairments is variable across patients, as patients can have one system impaired seemingly without having others affected, and the observed impairments may not be correlated with one another.

Imaging Correlates of Cognitive Impairments in Distinct Domains

Executive function, generally referring to higher cognitive tasks involving planning, initiating, and monitoring goal-directed behavior [McKinlay et al., 2010], is often regarded as the most common and profound cognitive deficit in patients with PD [Lewis et al., 2003; Zgaljardic et al., 2003]. Our results, from both FA and MD measures, revealed that executive dysfunction in PD was largely, yet not exclusively, associated with changes in DTI signal characteristics in frontal projection fibers, including the ACR, ALIC (connections between the frontal cortex, striatum, and thalamus), genu of corpus callosum (prefrontal connections between the two hemispheres), SFO (connections between frontal lobe and parietal lobe), and the sagittal stratum, which includes the inferior fronto-occipital fasciculus. These findings are consistent with a meta-analysis of neuroimaging and lesion studies in normal and non-PD subjects implicating these regions in executive function [Alvarez and Emory, 2006]. From recent DTI studies, parietal lobe associations in particular have been shown to involve executive functioning. In one normal aging DTI study, significant MD correlates were found in the white matter region adjacent to the inferior frontal gyrus and fronto-parietal parts of the superior longitudinal fasciculus [Sasson et al., 2012]. In another aging study, significant FA correlates were identified in bilateral areas extending from the prefrontal cortex to the parietal lobe, with projections to the anterior portions of the thalamus [Grieve et al., 2007].

Unlike executive function, significant correlations between attention and surrogate measures of microstructural integrity were found to be more widespread throughout the brain, engaging the most number of white matter tracts compared to the other domains. The widespread associations likely are in part attributable to the distributed nature of attentional networks, which include alerting, orienting, and executive attention components [Posner and Rothbart, 2007]. Although diffuse correlations were identified, the most significant associations with the attention domain were found in the left cingulate gyrus (cingulum) ($P < 0.001$) and splenium ($P = 0.001$). Diffusion abnormalities have previously been reported in the cingulum in patients with PD [Gattellaro et al., 2009; Kamagata et al., 2012; Karagulle Kendi et al., 2008].

Nonverbal memory impairment was associated with MD alterations in the fornix (short-term) and the right ACR (long-term). The fornix contains connections with the hippocampus, a major brain region crucial for memory functioning, and other structures associated with memory, including the anterior thalami, septal nuclei, and mammillary bodies. Our finding is in agreement with the current literature investigating the role of the fornix in memory [D'Esposito et al., 1995; Mielke et al., 2012; Thomas et al., 2011; Zhuang et al., 2012].

Finally, the results of the language domain revealed all frontal connecting white matter regions and considerably overlapped with the executive cognitive domain. One possible explanation for such overlap could be attributed to some of the similar neurocognitive tests used to assess the two domains. Measures of verbal fluency including letter fluency and category/animal fluency were used in both domains.

In general, across domains, MD in various subcortical regions was more strongly associated with performance in distinct cognitive domains than FA. FA and MD are thought to reflect different tissue characteristics, with FA sensitive to tissue directionality and organization, and MD to tissue density [Farina et al., 2000; Wiltshire et al., 2010]. Consistent with knowledge about the neurodegenerative processes of PD, the current results suggest that deterioration in cognitive function is related to a more severe general loss of axons/brain tissue than disruptions in tissue coherence.

Finally, although we hypothesized and largely observed that distinct cognitive domains are supported by different brain networks, we found the MD in the right ACR to be consistently related to performance in multiple domains (except the visuospatial domain). Given the commonality of this association across multiple domains, consideration should be given to an overriding phenomenon that may be pervasive and affecting performance in all domains. Specifically, we hypothesize that the association of ACR with motor performance may have adversely affected performance across multiple domains, independent of true function in each domain. This highlights the possibility that standardized tests designed in otherwise normal patient populations may not be directly applicable to diseased populations and may require cautious and expert interpretation by trained neuropsychologists. In the case of PD, an assessment tool specifically designed for PD may be more appropriate for capturing the wide spectrum of cognitive changes associated with this neurodegenerative disease. The PD-Cognitive Rating Scale (PD-CRS), for example, provides the best combination of acceptability, internal consistency, and test-retest and inter-rater reliability and includes assessments of both frontal-subcortical and instrumental-cortical function [Pagonabarraga et al., 2008].

METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

Different methodologies have been described for assessing the relevance and significance of FA and MD values in regions of white matter tracts. While the atlas-based

approach employed here does not account for all inter-subject anatomic variability, the white matter atlas used is a reliable and validated atlas and the described methodology is well accepted. The alternative approach of tract-based analyses necessitate deriving FA and MD values from within subject-specific MR tractography-derived white matter tracts (either whole tract or along-tract statistics). Given the underlying hypothesis that there are changes in FA and MD associated with changes in distinct neurocognitive domains, one could not assume that equivalent and comparable MR-tractography could be performed in differentially affected subjects and tracts. Perhaps the most significant shortcoming of the current cross-sectional analysis relates to limitations of sample size. Yet, it provides a preliminary assessment and confirmation of the hypothesis that impairments in distinct cognitive domains are subserved by unique networks. A prospective longitudinal study with age-matched controls and a standardized neurocognitive battery that is specific for PD would be needed to enable us to better assess the timing of neuroanatomical changes relative to cognitive impairments and to validate whether the putative biomarkers could be used for early detection.

CONCLUSIONS

This study demonstrates that the pattern of cognitive impairments seen in patients with PD is heterogeneous. While there are a few substructures that are implicated in impairment in multiple domains, microstructural changes as measured using DTI was mostly region specific to the function investigated. This mapping of subcortical networks may provide insight into the etiology of cognitive impairment in PD as well as provide guidance for future studies to identify early imaging biomarkers of cognitive impairment.

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