Microstructural White Matter Alterations in Patients With Drug Induced Parkinsonism

Yoonju Lee,[1] Yong Ho Choi,[2] Jae Jung Lee,[3] Hye Sun Lee,[4] Young H. Sohn,[1] Jong-Min Lee,[2] and Phil Hyu Lee [1,5]*

[1]*Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea*
[2]*Department of Biomedical Engineering, Hanyang University, Seoul, South Korea*
[3]*Department of Neurology, Inje University College of Medicine, Ilsan Paik Hospital, Goyang, South Korea*
[4]*Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, South Korea*
[5]*Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, South Korea*

Abstract: Drug-induced parkinsonism (DIP) is the second most common etiology of parkinsonism. And yet, there is little information on structural imaging in DIP to elucidate the accurate underlying pathomechanisms. To investigate microstructural white matter (WM) in patients with DIP using diffusion tensor image and to determine its relationship to severity of parkinsonian motor symptoms and cognitive function. A total of 42 patients with DIP, 65 with Parkinson's disease, and 33 control subjects were recruited from a movement disorders outpatient clinic. We performed comparative analysis of fractional anisotropy (FA) and mean diffusivity (MD) values among groups using tract-based spatial statistics. Correlation analysis between WM integrity and parkinsonian motor symptoms and cognitive performance was also performed in DIP patients using voxel-wise statistical analysis. DIP patients had significantly lower FA and higher MD values over widespread WM areas than control subjects. The patients with DIP had poor cognitive performance relative to control subjects, which correlated well with WM properties. Additionally, the parkinsonian motor symptoms were negatively correlated with FA values. In contrast, exposure time to the offending drugs prior to the development of parkinsonism or duration of parkinsonism showed no significant association with FA or MD values. The present study demonstrates that disruption of the WM microstructure is extensive in patients with DIP, and it is correlated with clinical parameters of parkinsonism and cognitive performance. This suggests that DIP may be reflective of underlying abnormality of microstructural WM. *Hum Brain Mapp 38:6043–6052, 2017.*

Key words: drug induced parkinsonism; diffusion tensor image; white matter; microstructure; fractional anisotropy; mean diffusivity

Additional Supporting Information may be found in the online version of this article.

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*Correspondence to: Phil Hyu Lee, Department of Neurology, Yonsei University College of Medicine 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, South Korea. E-mail: phlee@yuhs.ac

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INTRODUCTION

Drug-induced parkinsonism (DIP) is the second most common etiology of parkinsonism, especially in the elderly [Barbosa et al., 2006; Benito-Leon et al., 2003], comprising 10 to 30% of all cases of parkinsonism [Benito-Leon et al., 2003; Wenning et al., 2005]. Patients with DIP (6.8%) can be misdiagnosed with Parkinson's disease (PD) because the clinical manifestations of the two diseases are quite similar [Esper and Factor, 2008], including high frequency of tremor and asymmetrical signs [Marti-Masso and Poza, 1998]. Moreover, there is growing evidence that DIP patients have cognitive impairments [Ahn et al., 2015; Kim et al., 2011].

Although most patients with DIP are free of parkinsonism after discontinuation of the offending drug, parkinsonism can reappear after recovery in 6 to 10% of patients [Burn and Brooks, 1993; Kim et al., 2013], persist and eventually worsen after discontinuation of the offending drug [Brigo et al., 2014; Erro et al., 2015]. Additionally, dopamine transport (DAT) positron emission tomography (PET) studies showed that about one-third to half of DIP cases had underlying nigrostriatal dopaminergic dysfunction [Burn and Brooks, 1993; Lorberboym et al., 2006; Tolosa et al., 2003]. The pathological study provided evidence that neuroleptics can unmask preclinical PD in patients insufficient substantia nigra (SN) damage for the disease to manifest clinically [Shuaib et al., 2016]. Moreover, we recently demonstrated that a comparative quantitative analysis of the DAT activity in each striatal subregion showed that the early-onset DIP group had decreased DAT activities in several striatal subregions (not yet published). A functional magnetic resonance images (fMRI) analysis reported that DIP patients had decreased resting state functional connectivity within the executive control network in frontal and parietal areas, as well as decreased caudate-cortical functional connectivity [Ham et al., 2015]. These clinical and neuroimaging findings suggest that DIP patients may have abnormalities in nigral dopaminergic and extranigral systems. However, there is little information on structural imaging in patients with DIP to elucidate the accurate underlying pathomechanisms.

Diffusion tensor image (DTI) has been developed to investigate microstructural white matter (WM) alterations by measuring the orientation and direction of water molecules in neural tissue [Basser et al., 1994]. Microstructural WM alteration is evident even in the preclinical stage in the several neurodegenerative diseases, such as Alzheimer disease and PD [Davatzikos et al., 2008; Rolheiser et al., 2011]. In addition, microstructural WM alteration seems to differ depending on the underlying pathologies causing cognitive impairment or motor abnormality in the neurodegenerative diseases [Perea et al., 2013]. Thus, DTI is a useful tool to evaluate underlying WM involvement in patients with DIP. In the present study, we hypothesized that DIP would be closely associated with microstructural changes as a neuroanatomical correlate. To do this, we investigated WM alteration using DTI analysis in patients with DIP group compared with the patients with PD and healthy controls. Furthermore, we performed correlation analysis between WM alternations and clinical variables such as parkinsonian motor severity, cognitive performance and treatment parameter, which are important aspects encompassing DIP patients.

MATERIALS AND METHODS

Subjects

We retrospectively enrolled 42 patients with DIP, 65 patients with PD, and 33 healthy control subjects who were recruited from Yonsei University Severance Hospital between September 2011 and March 2015. DIP was diagnosed using the following four criteria [Jimenez-Jimenez et al., 1996]: (1) the presence of at least two of the four cardinal signs of parkinsonism, (2) the absence of extrapyramidal disorders prior to treatment with the offending drugs, (3) the onset of parkinsonism during the course of treatment with the offending drugs, and (4) disappearance or significant improvement in parkinsonism after cessation of the offending drugs. To improve diagnostic accuracy and eliminate patients with subclinical PD, we included DIP patients with normal DAT uptake on the putamen in [^{18}F] N-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) PET imaging. We included the PD group in the present study because the DIP might be a preclinical stage of PD [Marti-Masso and Poza, 1998]. PD was diagnosed according to the clinical criteria of the United Kingdom PD Society Brain Bank [Hughes et al., 1992] and presence of DAT uptake defects on FP-CIT PET scans. Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part III (UPDRS-III). All subjects had scores of cross-cultural smell identification test (CCSIT). Cognitive function was evaluated by the Seoul Neuropsychological Screening Battery [Kang and Na, 2003], which is a detailed neuropsychological (NP) test. For these, the quantifiable tests comprised the digit span (forward and backward), and stroop test (word and color reading of 112 items during a 2-min period) for attention/working memory, the Korean version of the Boston Naming Test for language, Rey Complex Figure Test (copying) for visuospatial function, Seoul Verbal Learning Test and Rey Complex Figure Test (immediate recall, 20-min delayed recall, and recognition) for verbal and visual memory, and phonemic and semantic Controlled Oral Word Association Test for frontal/executive function. We used composite score that is expressed as the sum of the standardized *Z*-score in each cognitive domain. Psychopathology (anxiety, depression, or sleep disorder) was assessed using the Korean version of neuropsychiatric inventory performed at the first visit [Choi et al., 2000]. Exclusion criteria included evidence of focal brain lesions or severe WM hyperintensities (the Manolio's scale score

>5) based on MRI [Manolio et al., 1994], which might be help to rule out patients with vascular parkinsonism, evidence of parkinsonian plus syndromes, and a diagnosis of dementia. We also investigated a history of cerebrovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and smoking). Members of the control group had no active neurologic disorders and no cognitive complaints based on a score ≥27 on the Korean version of mini-mental state examination (K-MMSE).

Standard Protocol Approvals, Registrations, and Patient Consents

We received approval for this study from the Yonsei University Severance Hospital ethical standards committee on human experimentation for experiments using human subjects.

MR Imaging Acquisition, Data Processing, and DTI Analysis

Image acquisition

All scans for all subjects were acquired using a Philips 3.0T scanner (Philips Intera; Philips Medical System, Best, The Netherlands). High-resolution T1-weighted MRI volumes were acquired axially using three-dimensional gradient echo sequence with the following parameters: 224 × 224 acquisition, 256 × 256 reconstructed matrix with 182 slices, 220 mm field of view, 0.859 × 0.859 × 1.2 mm^3 voxels, echo time (TE) 4.6 ms, and repetition time (TR) 9.7 ms. DTIs were obtained using single-shot echo-planar acquisition from 45 noncollinear, noncoplanar diffusion encoded gradient directions with the following parameters: 128 × 128 acquisition matrix with 70 slices, 220 mm field of view, 1.72 × 1.72 × 2 mm^3 voxels, TE 60 ms, TR 7.384 s, *b*-factor of 600 s/mm^2, no cardiac gating.

Data processing

Diffusion Toolbox from FMRIB's Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl) was used to preprocess all of diffusion weighted MRIs. To extract brain tissues, the skull of non-diffusion image was removed using Brain Extraction Tool [Smith, 2002]. Eddy current distortions were corrected by aligning each diffusion weighted image to nondiffusion image using affine transform for individual. Then, we extracted translation and rotation from affine transform to quantify head motion. Subsequently, diffusion tensors, including FA and MD were reconstructed for each voxel using DTIFIT from FSL. All of FA data were aligned to the FMRIB58_FA template using FMRIB's Nonlinear Registration Tool from FSL. Then mean FA image was created and skeletonized to represent center of WM tract of the group. The mean skeleton image was threshold at FA values above 0.2. Each FA images were projected onto this skeleton mask. The same transform and warped filed were applied to individual MD images [Smith et al., 2006]. The mean FA and MD values of these regions were found to be normally distributed across individuals in all comparison tests using Shapiro-Wilk normality test.

Statistical analysis of DTI data

For voxel-wise statistical analyses, nonparametric permutation test in Randomize Tool was used over 5,000 permutations [Nichols and Holmes, 2002]. First of all, Analysis of covariance adjusted for age, gender, and the motion parameters (translation, rotation) was performed among DIP, PD, and control groups and pairwise *t*-tests were run for post hoc comparisons. Using general linear models, voxel-wise correlation analyses were performed between DTI indices and clinical parameters, including composite score of each cognitive domain, UPDRS III score, disease duration, and exposure time to offender. To identify whether the linear relationship between the DTI indices and composite score of each cognitive domain differs between DIP patients and control subjects, interaction analyses were performed. Correction for multiple comparisons was estimated using threshold-free cluster enhancement [Smith and Nichols, 2009]. Level of significance was set at $P_{FWE} < 0.05$.

Statistical Analysis

All data are expressed as means (standard deviations). Demographic characteristics and NP test were compared using χ^2 test, Fisher's exact test, *t*-test, and analysis of variance followed by the Bonferroni post hoc test. *P* values were corrected for multiple comparisons using Bonferroni in comparison with composite scores among the groups. Statistical analyses were performed using commercially available software (SPSS, Inc., Chicago, IL, Ver. 23.0), and a two tailed $P < 0.05$ was considered significant.

RESULTS

Demographic Characteristics

Demographic characteristics of the patients are shown in Table I. No significant differences in age, gender, education years, vascular risk factors, WM hyperintensities, or motion status during DTI scanning were found among the three groups. The K-MMSE score was lower in the DIP group than control group ($P < 0.001$). Duration of Parkinsonism and UPDRS III did not differ significantly between the PD and DIP groups. Mean CCSIT score was lower in patients with PD than those with DIP ($P < 0.001$). In the DIP group, the number of patients complaining of depression, anxiety, or sleep disorder was significantly higher than other groups. Offending drugs in patients with DIP were gastrointestinal (GI) prokinetics (n = 21), L-type calcium channel blocker (CCB) (n = 7), antipsychotics (n =

TABLE I. Demographic characteristics of patients with drug induced parkinsonism (DIP), Parkinson's disease (PD) and controls

Characteristics	DIP (n = 42)	PD (n = 65)	Controls (n = 33)	P	F	χ^2	t	df
Age	67.9 (7.8)	69.1 (7.3)	70.4 (6.3)	0.338	1.095	–	–	139
Male cases (%)	10 (24)	20 (31)	10 (30)	0.739	–	0.669	–	2
Education years	8.4 (3.9)	9.3 (4.7)	10.1 (5.7)	0.285	1.266	–	–	139
K-MMSE	26.5 (2.3)	26.7 (2.1)	28.6 (1.3)	<0.001[a]	12.232	–	–	139
Vascular risk factor, n (%)								
Hypertension	20 (48)	27 (42)	15 (46)	0.840	–	0.406	–	2
Diabetes mellitus	14 (20)	8 (14)	5 (15)	0.788	–	0.505	–	2
Hyperlipidemia	9 (13)	12 (20)	6 (18)	0.414	–	1.730	–	2
Smoking	2 (3)	4 (7)	0 (0.0)	0.314	–	2.315	–	2
Neuropsychiatric inventory, n (%)[b]								
Depression	17 (71)	20 (32)	7 (21)	<0.001	–	16.116	–	2
Anxiety	11 (46)	14 (22)	4 (12)	0.010	–	8.890	–	2
Sleep disorder	9 (38)	16 (25)	3 (9)	0.034	–	6.584	–	2
WMH score (0–9 scale)	1.71 (0.81)	1.75 (1.03)	1.73 (0.76)	0.974	0.026	–	–	139
Motion during scanning								
Translation (mm)	1.89 (0.78)	1.80 (0.74)	1.97 (0.64)	0.636	0.455	–	–	139
Rotation (degree)	0.46 (0.27)	0.41 (0.21)	0.39 (0.15)	0.552	0.598	–	–	139
Disease duration (mo)	25.5 (74.5)	20.6 (19.7)	–	0.609	3.839	–	−0.512	105
UPDRS III	20.0 (8.8)	22.7 (8.5)	–	0.160	0.213	–	1.439	94
CCSIT	8.5 (2.2)	6.1 (2.2)	–	<0.001	0.041	–	−5.041	98

Numerical values are presented as mean (standard deviation or percentage).

[a]After a Bonferroni correction, the P values between the DIP and the control group and between the PD and the control group were less than 0.001, respectively.

[b]The number of patients undergoing Neuropsychiatric inventory was 24 in the DIP group, 63 in the PD group, and 33 in the control group. The significant results of post-hoc analysis were as follows. The P values between the DIP and the PD groups were 0.001 and 0.03 in the depression and anxiety mood, respectively. The P values between the DIP and the control groups were <0.001, 0.004 and 0.009 in the depression, anxiety and sleep disorder, respectively.

DIP, drug induced parkinsonism; PD, Parkinson's disease; K-MMSE, Korean version of mini-mental state examination; WMH, white matter hyperintensity; UPDRS III, Unified Parkinson's Disease Rating Scale, part III; CCSIT, cross-cultural smell identification test; df, degree of freedom.

7), serotonin selective receptor inhibitors (SSRI) (n = 5), serotonin and noradrenaline reuptake inhibitors (SNRI) (n = 1), and an antiarrhythmic drug (n = 1). GI prokinetics have been used for improving GI motility and CCBs for headache or dizziness. The patients who were taking antipsychotics have been diagnosed as schizophrenia (n = 2), psychotic disorder not otherwise specified (NOS) (n = 4) and anxiety disorder (n = 1). DIP patients with SSRIs and SNRIs have been diagnosed as depression (n = 4) and anxiety disorder (n = 2). The demographic characteristics of DIP patients who performed the NP test were similar to those of whole subjects and are presented in the Supporting Information Table I.

Comparison of FA and MD Values Among DIP, PD, and Control Subjects

Compared with the control subjects, patients with DIP had significantly lower FA and higher MD values in widespread WM areas, especially frontal areas (Fig. 1A,B). There were no significant clusters in which the DIP group had higher FA or lower MD values than the PD group. In addition, the PD group exhibited lower FA and higher MD values over extensive WM areas, mainly involving frontal and parietal areas, relative to the control group (Supporting Information Fig. 1A,B). There were no significant clusters in which the DIP or PD groups had higher FA or lower MD values than the control group. In a direct comparison of DIP and PD groups, there were no areas where FA and MD values differed significantly between the two groups.

In addition, we performed subgroup analysis of patients with GI prokinetics-induced DIP to examine the pattern of WM microstructural alterations in a homogenous DIP group. Relative to control subjects, patients with GI prokinetics-induced parkinsonism had lower FA and higher MD values in widespread WM areas, where significant clusters were mainly located in frontal areas (Fig. 2A,B). In a comparison between the GI prokinetics group (n = 21) and other DIP patients (n = 21), there were no areas where FA and MD values differed significantly between the two groups. Moreover, to exam the pattern of DTI according to psychopathology, we performed comparative analysis between patients with (n = 13) and without psychopathology (psychosis, anxiety disorder, or depression) (n = 29)

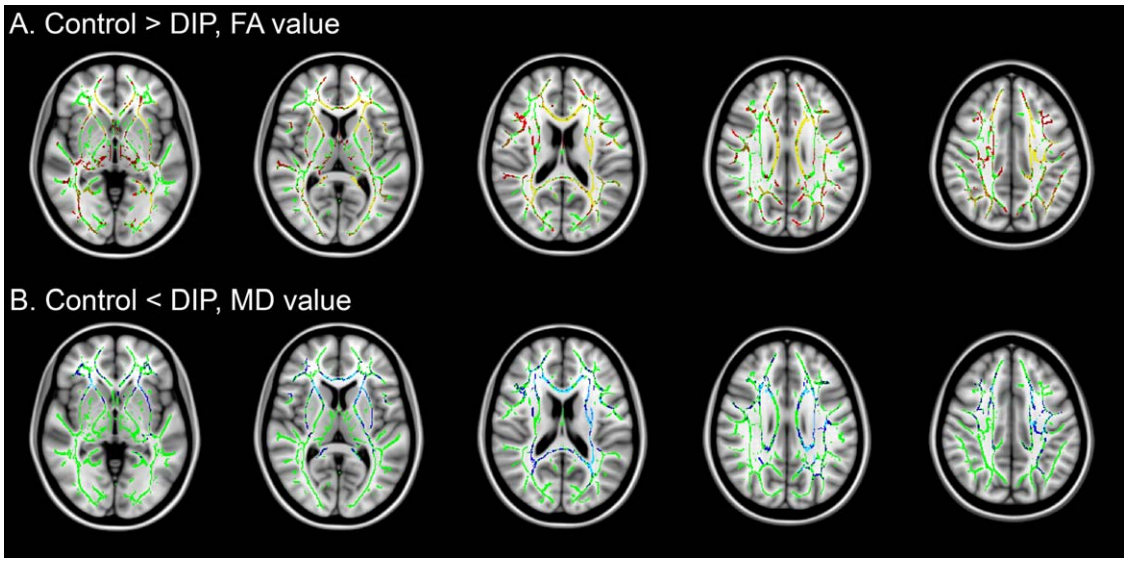

Figure 1.

Comparison of white matter (WM) properties between drug induced parkinsonism (DIP) and control groups. WM maps showing areas of decreased fractional anisotropy (FA) (red, $P_{FWE} < 0.05$; yellow, $P_{FWE} < 0.01$) and increased mean diffusivity (MD) (blue, $P_{FWE} < 0.05$; light blue, $P_{FWE} < 0.01$) on the skeleton mask (green). Compared with the control group, the DIP group showed (**A**) decreased FA and (**B**) increased MD across the widespread WM. [Color figure can be viewed at wileyonlinelibrary.com]

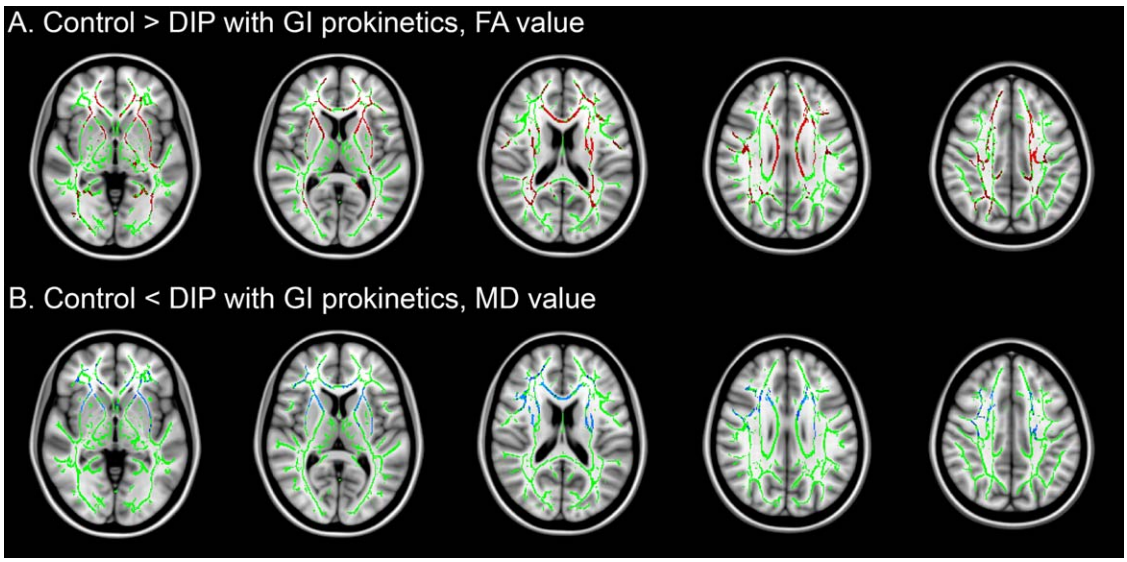

Figure 2.

White matter maps in drug induced parkinsonism (DIP) caused by gastrointestinal (GI) prokinetics. Compared with the control group, patients with GI prokinetics-induced parkinsonism showed (**A**) decreased fractional anisotropy (FA) (red, $P_{FWE} < 0.05$) and (**B**) increased mean diffusivity (MD) (blue, $P_{FWE} < 0.05$; light blue, $P_{FWE} < 0.01$) on the skeleton mask (green). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE II. Comparison of neuropsychological test among drug induced parkinsonism (DIP), Parkinson's disease (PD), and controls

Composite score	DIP (n = 24)	PD (n = 61)	Control (n = 28)	P	Corrected P[a]	Pair wise comparison: DIP vs. PD	DIP vs. control	PD vs. control	F	df
Attention/working memory	−1.69 (2.58)	0.32 (3.10)	1.29 (1.96)	0.001	0.006	0.010	0.001	N.S.	7.514	2
Language	−0.36 (1.01)	−0.34 (1.01)	0.47 (0.78)	0.001	0.006	N.S.	0.006	0.001	6.657	2
Visuospatial	−0.19 (1.87)	0.16 (1.01)	0.88 (0.51)	0.003	0.018	N.S.	0.004	0.026	8.016	2
Verbal memory	−0.47(2.57)	−0.18 (3.09)	1.74 (1.96)	0.005	0.030	N.S.	0.014	0.008	7.469	2
Visual memory	−0.59 (3.07)	−0.16 (2.98)	1.72 (2.48)	0.007	0.042	N.S.	0.014	0.016	6.987	2
Frontal executive	−1.67 (2.44)	−0.89 (2.34)	1.28 (2.77)	<0.001	0.004	N.S.	<0.001	0.001	11.093	2

Numerical values are presented as mean of composite score (standard deviation).
[a]Bonferroni corrected P values were used for multiple testing.
DIP, drug induced parkinsonism; PD, Parkinson's disease; N.S., nonsignificant; df, degree of freedom. Analyses were performed by analysis of variance and Bonferroni test for the post hoc analysis.

and between patients with (n = 9) and without axis I psychosis (schizophrenia, psychosis NOS, and major depressive disorder) (n = 33). There were no clusters where FA and MD values differed significantly between the subgroups.

Cognitive Performance and Its Relation With DTI Parameters in Patients With DIP

Compared with the control subjects, patients with DIP had lower composite scores with respect to attention/working memory, language, visuospatial, verbal and visual memory function, and frontal/executive function. Similarly, patients with PD exhibited lower composite scores in all cognitive domains compared to the control subjects. In a direct comparison, patients with DIP showed a lower composite score in attention/working memory relative to the PD patients (Table II). Detailed NP test results for the groups are shown in Supporting Information Table II. In voxel-wise correlation analysis, composite Z-scores in attention/working memory, language, and verbal and visual memory were positively associated with FA values in widespread WM, where WM properties in the cingulate gyrus and genu of the corpus callosum had a strong association with composite scores in those domains (Fig. 3A–D). Visuospatial and frontal/executive composite scores had a weak correlation with FA values of frontal and posterior cortical WM (Fig. 3E,F). Moreover, MD values were negatively correlated with attention/working memory composite scores (Fig. 3G) and verbal and visual memory composite scores (Fig. 3H,I) in similar areas to where FA values showed a correlation in the same domains. In addition, we performed interaction analysis to examine interaction effect between group (DIP and control) and cognition. The interaction between group and cognitive composite scores in attention/working memory (FA values), visual memory (FA and MD values), verbal memory (FA values), and frontal/executive domain (FA values) is significant (Supporting Information Fig. 2).

Association Between FA Values and Motor Function in Patients With DIP

In correlation analysis, UPDRS motor score was negatively associated with FA values in frontoparietal WM, especially over the cingulate gyrus WM and genu of the corpus callosum WM ($P_{FWE} < 0.01$, Fig. 4).

Comparison of FA and MD Values in Patients With DIP According to Exposure Time to Offenders or Parkinsonism Duration

Next, we evaluated FA and MD values in patients with DIP according to exposure time to offending drugs and duration of parkinsonism. DIP patients with a long exposure time to the offending drugs had no significant differences in FA or MD values compared to those with a short drug exposure time. FA or MD values were not significantly different between DIP patients with a longer duration of parkinsonism and those with shorter parkinsonism. Additionally, voxel-wise correlation analysis showed that duration of parkinsonism prior to DTI scanning or exposure time to the offending drugs had also no significant association with FA or MD values in WM areas.

DISCUSSION

In this study, we demonstrated that DIP patients had significantly lower FA and higher MD values over widespread WM areas than control subjects, and that the FA values were negatively correlated with the severity of parkinsonian motor symptoms. Additionally, patients with DIP had poor cognitive performance, which correlated well with WM microstructural alterations. However,

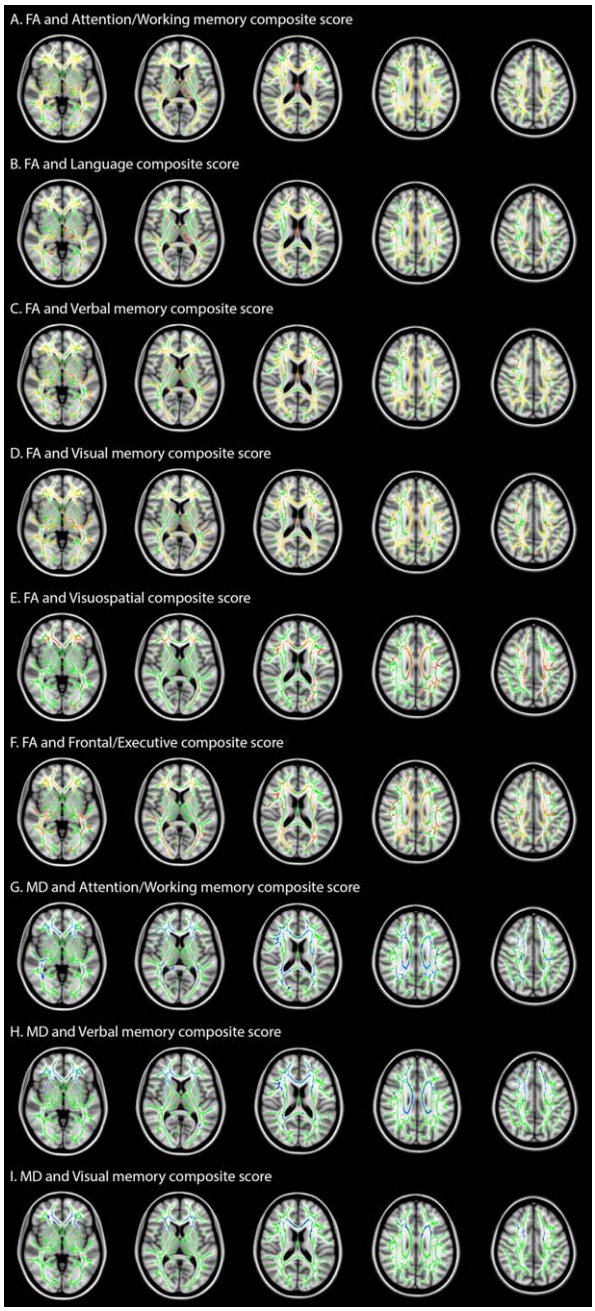

Figure 3.

Correlation analysis of cognitive performance and white matter properties in the drug induced parkinsonism patients. (**A**) Attention/working memory, (**B**) language, (**C**) verbal memory, (**D**) visual memory, (**E**) visuospatial, and (**F**) frontal/executive composite scores had a positive correlation with fractional anisotropy (FA) values in widespread white matter (red, $P_{FWE} < 0.05$; yellow, $P_{FWE} < 0.01$). (**G**) Attention/working memory, (**H**) verbal and (**I**) visual memory composite scores had a negative correlation with mean diffusivity (MD) values (blue, $P_{FWE} < 0.05$; light blue, $P_{FWE} < 0.01$). Green indicates the skeleton mask. [Color figure can be viewed at wileyonlinelibrary.com]

neither exposure time to the offending drugs nor duration of parkinsonism showed an association with the FAs or MDs. These data indicate that DIP may be closely associated with WM alterations, suggesting that DIP may be reflective of underlying microstructural WM properties.

This study showed that DIP patients had extensive microstructural WM alterations compared with the control subjects. In correlation analysis, FA values in the frontal and parietal areas were closely associated with parkinsonian motor severity in patients with DIP. Generally, macrostructural lesions of WM, such as WM hyperintensity, are independent contributors to the development of gait disturbance or motor compromise in the general population [Baezner et al., 2008]. WM lesions in PD patients also negatively influence parkinsonian motor behavior, thus PD patients with severe WM lesions have a shorter illness duration, more prominent bradykinesia, higher UPDRS scores, higher progression index, and less response to dopaminergic treatment than those with less severe WM lesions [Lee et al., 2009; Piccini et al., 1995; Sohn and Kim, 1998]. Although the underlying mechanism is not yet fully understood, WM lesions may disrupt the connections of functionally important basal ganglia-motor and sensory cortical circuits relevant to normal controls [Leuchter et al., 1994; Piccini et al., 1995] and induce cortical atrophy secondary to dying-back neuronal degeneration [Du et al., 2005; Esper and Factor, 2008; Leys et al., 1991]. Thus, microstructural WM alterations observed in patients with DIP may further deteriorate motor control in addition to causing parkinsonian motor deficits secondary to dopaminergic deprivation. Consistent with our findings, a DTI analysis in patients with schizophrenia reported that the severity of tardive dyskinesia was correlated with FA reduction in the fronto-striatal circuit [Bai et al., 2009]. Accordingly, dopamine blocking agent-related movement disorders, such as DIP and tardive dyskinesia, appear to share a common pathophysiology in the abnormality of WM.

Another interesting finding of this study is that patients with DIP showed poor performance in all cognitive subdomains relative to control subjects. Additionally, the DIP group had poorer cognitive performance in attention/working memory than the PD group. These findings are consistent with those of previous reports that focused on cognitive dysfunction in DIP. In a small case series, patients with DIP had cognitive impairment in all items of cognitive domain in NP tests compared to the control group, and in the contrast program compared to the PD group [Kim et al., 2011]. Another study reported that all patients with GI prokinetics-induced parkinsonism exhibited dementia or mild cognitive impairment [Ahn et al., 2015]. In a recent fMRI study, we found that DIP patients had decreased cortical functional networks within executive control networks compared to control or PD subjects [Ham et al., 2015]. FMRI results imply that dopamine blocking agents might have an inhibitory influence on

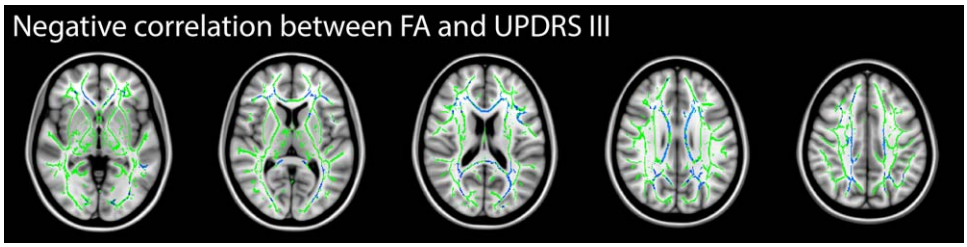

Figure 4.
Correlation analysis of UPDRS motor score and white matter properties in the drug induced parkinsonism patients. Unified Parkinson's Disease Rating Scale (UPDSRS) III scores had a negative correlation with fractional anisotropy (FA) (blue, $P_{FWE} < 0.05$; light blue, $P_{FWE} < 0.01$) on the skeleton mask (green). [Color figure can be viewed at wileyonlinelibrary.com]

cortical dopaminergic neurons that are closely engaged in a wide range of externally directed tasks [Seeley et al., 2007]. Taken together, the present DTI results provide further in vivo evidence of the presence of microstructural correlates of cognitive impairment in patients with DIP. In a correlation analysis, we found that the cognitive composite scores of all domains in DIP patients were positively associated with total FA values in extensive WM areas. Additionally, MD values were negatively correlated with attention/working memory and verbal and visual memory composite scores in similar areas to where FA values showed a correlation with these scores. Moreover, interaction between group and cognition was significant in attention/working memory, visual and verbal memory, and frontal/executive domain, indicating that the association of cognition and WM would differ between the DIP and control groups. No study has yet examined whether the microstructure of WM is a cognitive correlate in DIP; however, DTI studies in patients with PD have demonstrated that microstructural WM alterations might be closely associated with cognitive performance in the early stage of PD as well as other neurodegenerative diseases [Duncan et al., 2016; Hattori et al., 2012], suggesting a close relationship between WM properties and cognitive performance. Thus, along with neurochemical factors, it is possible that microstructural WM changes may be one of the anatomical correlates responsible for cognitive impairment in DIP patients.

To evaluate whether the pattern of WM microstructural changes differed depending on the species of offending drug, we performed subgroup analysis in DIP patients exposed to GI prokinetics. WM areas where FA or MD values were significantly altered were similar to those observed in all patients with DIP. Moreover, there was no significant difference in DTI patterns according to offending drug (GI prokinetics), psychopathology, or axis I psychopathology. These suggest that the pattern of microstructural WM alterations observed in DIP patients are not related to the species of offender or underlying pathology. In addition, we analyzed the relationship between clinical factors and FA or MD values to exam the cause-and-effect relationship between WM microstructure and DIP to the greatest extent possible. FA or MD values did not significantly differ according to exposure time to the offenders prior to the development of parkinsonism or duration of parkinsonism prior to DTI scan. If abnormality of WM microstructure resulted from offenders or related parkinsonism, we would have expected WM alterations to be greater in proportion to exposure time to the offenders or duration of parkinsonism. Consistent with our results, a recent clinicopathological report demonstrated that DIP patients already had neuronal degeneration in the substantia nigra [Shuaib et al., 2016]. A DAT study of DIP patients showed that the partially recovered DIP group had relatively lower ligand uptake in the striatum than completely recovered patients [Hong et al., 2016]. Although causality could not be inferred from cross-sectional data in this study, we cautiously speculate that microstructural WM alterations may be a preexisting pathology of DIP, and therefore act as a risk factor for DIP, rather than be a secondary phenomenon of dopamine depleting effects. However, a follow-up imaging study with a prospective design is required to definitively address this issue.

Finally, this study demonstrated no significant difference in DTI parameters between patients with DIP and PD. Several previous studies have reported that a history of DIP may be a risk factor for PD [Hardie and Lees, 1988; Kim et al., 2013]. An imaging study using DAT PET showed that persistent DIP is associated with subtle decrease in nigrostriatal dopaminergic system [Hong et al., 2016]. Additionally, a clinicopathological study demonstrated that dopamine blocking agents could unmask preclinical PD in patients with insufficient SN damage for the disease to manifest clinically [Shuaib et al., 2016]. Thus, it is speculated that DIP and PD may share common underlying pathomechanisms, possibly acting as a premotor marker for PD.

This study had several limitations. First, the dopaminergic blocking agents included in this study have been shown to induce parkinsonism via heterogeneous mechanisms. Additionally, underlying disease in DIP patients, such as psychotic disorder or depression could alter the WM microstructures [Kieseppa et al., 2010; Kubicki et al.,

2007]. Thus, we could not exclude completely the possibility that different offenders or underlying psychopathology affected DTI patterns, despite the similarity in DTI patterns between the subgroup of GI prokinetics-related DIP and the whole DIP group. Second, the possible inclusion of patients with atypical parkinsonian syndrome could not be completely excluded, because these patients have normal DAT uptake in the striatum [Jin et al., 2013] as well as microstructural alterations in extensive WM areas [Worker et al., 2014]. Finally, we could not recruit another group that did not develop parkinsonism even though they were exposed to the offenders for actual comparison with the patients with DIP.

CONCLUSION

This study demonstrated for the first time that disruption of the WM microstructure is extensive in patients with DIP, and that its severity is correlated with clinical parameters of parkinsonism and cognitive performance. This suggests that microstructural WM changes would be closely coupled with DIP; however, more studies are required to confirm that WM microstructure is a risk factor for DIP in a longitudinal study.

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