Olfactory Performance and Resting State Functional Connectivity in Non-demented Drug Naïve Patients with Parkinson's Disease

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Abstract: Olfactory performance in Parkinson's disease (PD) is closely associated with subsequent cognitive decline. In the present study, we analyzed the olfaction-dependent functional connectivity with a hypothesis that olfactory performance would influence functional connectivity within key brain areas of PD. A total of 110 nondemented drug-naïve patients with PD were subdivided into three groups of high score (PD-H, $n = 23$), middle score (PD-M, $n = 64$), and low score (PD-L, $n = 23$) based on olfactory performance. We performed the resting-state functional connectivity with seed region of interest in the posterior cingulate cortex (PCC) and caudate. An analysis of functional connectivity revealed that PD-L patients exhibited a significant attenuation of cortical functional connectivity with the PCC in the bilateral primary sensory areas, right frontal areas, and right parietal areas compared to PD-H or PD-M patients. Meanwhile, PD-L patients exhibited a significant enhancement of striatocortical functional connectivity in the bilateral occipital areas and right frontal areas compared to PD-H or PD-M patients. In the voxel-wise correlation analysis, olfactory performance was positively associated with cortical functional connectivity with the PCC in similar areas of attenuated cortical connectivity in PD-L patients relative to PD-H patients. On the other hand, the cortical functional connectivity with the caudate was negatively correlated with olfactory performance in similar areas of increased connectivity in PD-L patients relative to PD-H patients. The present study demonstrated that resting state functional connectivity exhibits a distinctive pattern depending on olfactory performance, which might shed light on a meaningful relationship between olfactory impairment and cognitive dysfunction in PD. *Hum Brain Mapp* 36:1716–1727, 2015. © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Olfactory dysfunction is a salient nonmotor feature of Parkinson's disease (PD), occurring in at least 90% of PD patients. It often manifests years before the development of parkinsonian motor symptoms, such as tremor, bradykinesia, rigidity, or gait disturbance [Ponsen et al., 2004]. Neuropathological studies have suggested that in addition to the enteric plexus, the olfactory system seems to be one of vulnerable sites of α -synuclein accumulation, and thus neurodegenerative changes in the olfactory system occur earlier in the course of PD [Braak and Del Tredici, 2008; Ponsen et al., 2004]. Olfactory performance in PD seems to be more closely associated with the nonmotor features such as sleep disturbance, cardiovascular and gastrointestinal problems, and neuropsychiatric dysfunction rather than the motor symptoms that are mediated by the nigrostriatal system [Doty, 2012; Lee et al., 2006; Stiasny-Kolster et al., 2005]. Importantly, recent evidence has demonstrated that olfactory dysfunction is associated with poorer performance on verbal memory and frontal executive tasks, and that diminished olfactory performance in the early stages of PD is associated with an increased risk of ongoing cognitive decline [Stephenson et al., 2010]. Among the cardinal motor and nonmotor symptoms of PD, severe olfactory dysfunction might be the most important indicator for the development of dementia within 3 years [Baba et al., 2012]. Therefore, poor olfactory performance in the early stages of PD is closely associated with subsequent cognitive decline.

Recently, resting-state functional magnetic resonance imaging (fMRI) has been used widely to investigate brain function under both normal and pathological conditions, because it provides a good signal to noise, requires minimal patient compliance, avoids potential confounding performance related to cognitive tasks, and is a noninvasive technique that is easily used in clinical studies [Fox and Greicius, 2010]. During rest, low-frequency blood-oxygen level fluctuations within a specific frequency range (0.01–0.08 Hz) are considered to be related to spontaneous neuronal activity [Cordes et al., 2001; Fransson, 2005]. Thus, analysis of resting-state networks (RSNs) offers a means with which to evaluate the status of functional systems within the brain without externally goal-directed cognitive performance [Mantini and Vanduffel, 2013]. Compared to healthy controls, PD patients exhibit disruptions of functional network connectivity within corticostriatal loops, as well as decreased functional integration across neuronal networks that involve the striatum, mesolimbic cortex, and sensorimotor regions [Hacker et al., 2012; Luo et al., 2014]. Furthermore, there is ample evidence that altered resting

state functional connectivity is associated with cognitive status in Alzheimer's disease and dementia with Lewy bodies, as well as PD [Galvin et al., 2011; Rektorova et al., 2012]. In the present study, we hypothesized that olfactory performance as a predictor of cognitive impairment influences the functional connectivity within key brain areas of patients with PD. To examine this, we investigated the pattern of resting state functional connectivity in patients with PD according to olfactory performance to further elucidate olfactory-dependent cortical-subcortical functional networks.

METHODS

Subjects

The study participants were 110 nondemented drug naïve patients with PD and 20 normal healthy subjects (mean age, 66.3; 9 men) who were recruited consecutively from July 2011 to September 2013 at a university hospital. Odor identification was assessed with a cross-cultural smell identification (CCSI) test [Double et al., 2003], which been used to assess olfactory function in PD patients in a number of countries [Lee et al., 2006; Rodríguez-Violante et al., 2011]; a high score indicated good olfactory performance. According to the olfactory performance, subjects with PD were subdivided into three groups of high score (CCSI score ≥ 9 , $n = 23$; PD-H), middle score ($5 \leq$ CCSI score < 8 , $n = 64$; PD-M), and low score (CCSI score ≤ 4 , $n = 23$; PD-L). PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank. To ensure clinical diagnostic accuracy, only the patients who displayed decreased dopamine transporter uptake in the posterior putamen on a ^{18}F -fluorinated-N-3-fluoropropyl-2- β -carboxymethoxy-3- β -(4-iodophenyl)nortropane positron emission tomography scan were included in this study. Motor symptoms were assessed using the unified PD rating scale part III (UPDRS-III). The exclusion criteria included evidence of cognitive dysfunction compatible with the clinical diagnostic criteria for probable PD dementia [Emre et al., 2007], evidence of focal brain lesions based on MRI, evidence of Parkinson plus syndrome or drug induced parkinsonism (antipsychotics, gastrointestinal kinetics, antiepileptic drugs, or L-type calcium channel blockers), or Beck Depression Inventory (BDI) score > 21 . The Seoul neuropsychological screening battery (SNSB) [Kang, 2003], a detailed neuropsychological test, was used to evaluate cognitive performance. The SNSB includes the cognitive subsets of *attention* (forward and backward digit span), *language and related functions* (the Korean version of the Boston Naming Test and repetition),

visuospatial function (drawing an interlocking pentagon and the Rey complex figure test [RCFT]), *verbal memory* (the Seoul Verbal Learning Test; immediate recall, 20 min delayed recall, and recognition), *visual memory* (the RCFT; immediate recall, 20 min delayed recall, and recognition), and *frontal executive function* (contrasting program, go-no-go test, phonemic and semantic Controlled Oral Word Association Test, and Stroop test). Abnormal cognitive performance in each cognitive subdomain was defined as a score below the 16th percentile of the norm. Age-, sex-, and education-specific norms for each test based on 447 normal subjects are available. All subjects with PD had scores of the Korean version of the mini-mental state examination (K-MMSE) above the 16th percentile for the age- and education-appropriate norm, and no evidence of abnormal activities of daily living, measured by a Korean instrumental activities of daily living scale [Cho et al., 2008]. Members of the control group had no active neurologic disorders and no cognitive complaints with a minimal score on the K-MMSE of 25. This study was approved by the Yonsei University Severance Hospital ethical standards committee on human experimentation for experiments using human subjects.

MR Imaging Analysis

Image acquisition

All participants underwent functional MRI (fMRI) scanning with a 3.0 Tesla MRI scanner (Achieva, Philips Medical System, Best, Netherlands) to obtain T2* weighted single shot echo planar imaging sequences. Each participant was axially scanned using the following parameters: voxel size, $2.8 \times 2.8 \times 3.0 \text{ mm}^3$; slice number, 31 (interleaved); matrix, 80×80 ; slice thickness, 3.0 mm; gap, 1.0 mm; repetition time (TR), 2000 ms; echo time (TE), 30 ms; flip angle = 90° ; and field of view, 220 mm. Each 330-sec scan produced 165 fMRI images, which is known to be sufficient to evaluate resting state functional connectivity [Van Dijk et al., 2010] and to obtain low frequency oscillation for the resting state functional connectivity. During functional MR imaging, the subjects were instructed to stay awake with their eyes closed, without focusing on a specific thought and without moving.

Cortical thickness analysis

All procedures were automatically processed using CIVET-Montreal neurological institute (MNI) image processing software to produce the cortical surface and to measure the cortical thickness. First, we performed an N3 algorithm to correct nonuniform artifacts [Sled et al., 1998]. The corrected images were registered in a standardized stereotaxic space by linear transformation [Collins et al., 1994] and were classified into white matter, gray matter, cerebrospinal fluid, and background using an artificial neural net classifier [Zijdenbos et al., 1996]. Surfaces of the gray matter

and white matter were extracted automatically using a constrained Laplacian-based automated segmentation with proximities algorithm [Kim et al., 2005; MacDonald et al., 2000]. Cortical thickness was calculated as the Euclidean distance between correspondence vertices of the white matter and gray matter surfaces after applying an inverse transformation matrix to cortical surfaces [Lerch and Evans, 2005]. To measure the cortical thickness of corresponding region between subjects, an improved nonlinearly surface registration algorithm and an unbiased iterative group template were employed [Lyttelton et al., 2007]. Each subject's cortical thickness maps were blurred using a 20 mm full-width at half-maximum (FWHM) with surface-based diffusion smoothing [Lerch and Evans, 2005]. Then all cortical thicknesses of whole brain vertices were averaged.

Preprocessing of resting-state fMRI data

Preprocessing of resting-state fMRI data was carried out using Analysis of Functional NeuroImages, (<http://afni.nimh.nih.gov/afni>) software [Cox and Jesmanowicz, 1999]. The first five volumes from each functional image were discarded to allow for stabilization of the magnetic field. Images were despiked, and then corrected for slice time acquisition differences and head motion [Cox and Jesmanowicz, 1999]. At the motion-correction stage, displacement due to head motion was estimated using the motion-correction parameters of the x , y , and z translations and three rotation axes. In all subjects, estimated displacement due to head motion was less than 1 mm between successive time-series volumes and less than 2 mm in any of the three translation directions or less than 2.0° maximum rotation around any of the axes during the resting-state scans. Then, the slice-timing and motion corrected functional images were performed using the anatomy based correlation corrections (ANATICOR) method [Jo et al., 2010]. Data were regressed out as follows: (1) by six parameters obtained by rigid body correction of head motion, (2) by the signal from the eroded large ventricle mask, and (3) by the signal from a region of the local white matter erosion mask ($r = 15\text{mm}$). Hardware artifacts were modeled with eroded local white matter and erode large ventricle masks. To obtain the large ventricle masks and white matter mask, the registered and nonuniformity corrected T1 images were classified into white matter, gray matter, cerebrospinal fluid, and background using an advanced neural-net classifier [Zijdenbos et al., 1996]. Additionally, four large ventricles were automatically identified using automated nonlinear image matching and anatomical labeling, a well-established nonlinear warping algorithm that uses a multiscale approach to deform one image to match a previously labeled template [Collins et al., 1995]. Then, the anatomical T1 image was coregistered to the functional images using the affine registration with Local Pearson Correlation cost function [Saad et al., 2009], and all masks were transformed to echo planar imaging space. To reduce partial volume effects, the white

matter mask and the large ventricle mask were eroded by one voxel. Subsequently, data were temporally band-pass filtered ($0.009 < f < 0.08$) to remove scanner drift and physiological noise. Data were then masked out using the gray matter mask to reduce the inclusion of unwanted blood oxygen level-dependent (BOLD) or other physiological signals that occur due to large draining vessels that tend to course on the outer surface of gray matter. Images were normalized to a standard MNI152 template and resampled at an isotropic voxel size of 2 mm before spatial smoothing was carried out with a 6-mm FWHM Gaussian kernel.

Functional connectivity analyses

Two regions of interest (ROIs) were defined to study olfactory-dependent resting-state functional networks in patients with PD. First, the posterior cingulate cortex (PCC) was chosen to investigate alterations within the default mode network (DMN), which is highly associated with cognitive function in resting-state fMRI analyses. This ROI was defined using voxels with a 6-mm radius spherical mask at the peak voxel ($x/y/z = 0/-52/30$ mm) [Hahn et al., 2012]. Second, the caudate, which had been known as a key subcortical structure in cognitive corticostriatal loop, was selected to study functional connectivity between the basal ganglia and cerebral cortices [Kwak et al., 2010]. This area was defined according to the automated anatomical labeling template [Tzourio-Mazoyer et al., 2002]. The time series for data in each ROI were averaged, and Pearson's correlation coefficient maps were created for each individual subject. The correlation coefficient maps were converted to a z-value using Fisher's z transformation.

Group comparisons

Individual z values were entered into a one-sample *t*-test in a voxel-wise statistics to investigate brain regions showing significant functional connectivity with each seed in the resting state within each group. We obtained a corrected significance level of $P_{\alpha} < 0.05$ (uncorrected threshold of $P < 0.00001$ with 16 voxel). To determine the differences of functional connectivity between the three groups, an analysis of covariance was performed using age, sex, cortical thickness, and disease duration as covariates. Using the AFNI's AlphaSim program, Monte Carlo simulations were performed to control for Type I errors (parameters: individual voxel *P*-value = 0.02, simulated 10,000 times iteratively, 6-mm FWHM Gaussian filter width with a whole-brain mask). The AlphaSim program provides an estimate of the overall significance level achieved for various combinations of individual voxel probability thresholds and cluster size thresholds [Poline et al., 1997]. The group-specific gray matter mask created using individual normalized gray matter masks. We combined them to mask on group-specific gray matter mask. We obtained a corrected significance level of $P_{\alpha} < 0.05$

(uncorrected individual voxel height threshold of $P < 0.02$ with a minimum cluster size of $1,672 \text{ mm}^3$). Subsequently, to examine the intergroup differences, post hoc two-sample *t* tests were performed between pairs of groups for voxel-wise statistics (corrected significant level of $P_{\alpha} < 0.05$).

Correlation analysis of olfactory performance and resting-state functional connectivity

To investigate the relationship between the functional connectivity, we performed multiple regression analysis between the functional connectivity and CCSI scores in patient groups. Age, sex, cortical thickness, and disease duration were entered as covariates in the regression analysis. Additionally, a conjunction analysis was performed to display the overlap between statistical images showing group difference (PD-L vs PD-H) and those showing correlations with CCSI scores. The statistical maps were corrected for multiple comparisons to a significance level of $P_{\alpha} < 0.05$.

Statistical Analysis

All data are expressed as means (SDs). The analysis of variance test or the Chi Square test for continuous and categorical variables, respectively. A composite score, dividing the sum by number of tests in each cognitive domain, was used to form reliable measures and an analysis of covariance was used to compare the results of the neuropsychological tests among the groups using a multivariate analysis of variance with age, years of education, and PD duration as covariates. Post hoc analyses included a Bonferroni test performed to compare the means for the three groups. Statistical analyses were performed using commercially available software (SPSS, Ver.18.0), and a two tailed *P* value < 0.05 was considered significant.

RESULTS

Demographic Characteristics

The demographic characteristics of the patients are shown in Table I. No significant differences in age, gender, education level, duration of parkinsonism, UPDRS motor score, and BDI scores were found between the PD-L, PD-M, and PD-H groups. The mean CCSI score was 3.61 in the PD-L group, 6.72 in the PD-M group, and 9.52 in the PD-H group ($P = 0.001$). The mean K-MMSE score showed highest scores in the PD-H group and lowest scores in the PD-L, although the difference did not reach statistical significance. The mean intracranial volume (mm^3) and cortical thickness (mm) did not differ significantly among the groups (1,303,646.1, and 3.18 in the PD-L group, 1,307,842.1, and 3.11 in the PD-M group, 1,322,964.3, and 3.17 in the PD-H group, and 1,322,964, and 3.16 in the control group). The neuropsychological tests showed that

TABLE I. Demographic characteristics of Parkinson's disease patients according to olfactory performance

	PD-H (<i>n</i> = 23)	PD-M (<i>n</i> = 64)	PD-L (<i>n</i> = 23)	<i>P</i> -value
Age (yr)	62.3 (9.17)	66.6 (8.1)	64.1 (11.01)	NS
Gender (number of men, %)	11 (46.6%)	26 (47%)	12 (53.4%)	NS
Education levels (yr)	12.2 (3.6)	10.1 (3.4)	10.2 (4.8)	NS
Parkinsonism duration (mo.)	22.3 (14.5)	24.2 (35.9)	25.5 (18.9)	NS
UPDRS motor score	20.1 (8.9)	9.2 (1.3)	23.8 (7.2)	NS
CCSI	9.5 (0.7)	6.7 (1.0)	3.6 (0.6)	0.001
K-MMSE	28.0 (1.9)	26.9 (1.8)	27.0 (1.7)	NS
BDI	13.8 (10.4)	9.9 (5.8)	16.3 (9.9)	NS
Intracranial volume (mm ³)	1,303,646.1 (112,177.7)	1,307,842.1 (118,093.6)	1,322,964.3 (120,074.6)	NS
Cortical thickness (mm)	3.18 (0.15)	3.11 (0.16)	3.17 (0.13)	NS

Values are expressed as mean (standard deviation). PD-H = Parkinson's disease with high CCSI score; PD-M = Parkinson's disease with middle CCSI score; PD-L = Parkinson's disease with low CCSI score; CCSI = Cross-Cultural Smell Identification; K-MMSE = Korea version of the Mini-Mental State Examination; BDI = Beck Depression Inventory; UPDRS = unified Parkinson's disease rating scale; NS = not significant.

patients with PD-H tended to have higher scores in visuo-spatial, language, and frontal executive function tasks relative to patients with PD-L. No significant differences in specific cognitive subdomains were found between the PD-H and PD-M groups (Table II).

Comparison of Resting State Corticocortical Functional Connectivity between PD-L, PD-M, and PD-H Patients

To evaluate the cortico-cortical functional connectivity in patients with PD, the PCC was used as a seed for DMN analysis. The one sample *t*-test in the control and PD groups showed that brain regions including the bilateral frontal, temporal, occipital, and posterior splenial areas have positive functional connectivity with the PCC. Compared with the controls, the patterns of positive cortical functional connectivity with the PCC differed depending on olfactory performance. The PD-L patients had decreased cortical functional connectivity in the primary motor and sensory areas, right frontal area, and posterior

cortical areas involving the right supramarginal gyrus and left precuneus compared with the normal controls (Fig. 1A). The PD-M patients had decreased cortical functional connectivity in the right primary sensory area, right frontal area, and left precuneus relative to the controls (Fig. 1B). Meanwhile, there was no significant difference in the cortical functional connectivity from the PCC between the PD-H patients and normal controls. There were no areas of significantly increased cortical functional connectivity in the PD groups relative to the normal controls. In a direct comparison of the PD-L and PD-H groups, the PD-L patients exhibited decreased cortical functional connectivity with the PCC in the bilateral primary sensory areas, right superior parietal area, and right superior and middle frontal areas compared with the PD-H patients (Fig. 1C). In a direct comparison of the PD-L and PD-M groups, the PD-L patients had a similar pattern of decreased functional cortical connectivity with the PCC relative to the PD-M patients; however, the extent of decreased connectivity was less prominent (Fig. 1D). In a comparison of the PD-M and PD-H groups, the PD-M patients had small clusters of decreased cortical connectivity with the PCC in

TABLE II. Neuropsychological data in Parkinson's disease patients according to olfactory performance

Test	PD-H	PD-M	PD-L	<i>P</i> -value ^a	PD-H vs. PD-M ^b	PD-M vs. PD-L ^b	PD-H vs. PD-L ^b
Attention	7.1 (1.3)	7.0 (1.5)	6.6 (1.5)	NS	NS	NS	NS
Language and related function	31.4 (3.9)	28.7 (5.1)	28.2(3.7)	0.046	NS	NS	0.059
Visuospatial function	16.7 (1.2)	16.3 (2.3)	14.8 (4.0)	0.038	NS	NS	0.041
Verbal memory function	14.7 (3.4)	15.3 (2.5)	12.9 (3.3)	0.027	NS	0.028	NS
Visual memory function	16.0 (5.1)	15.7 (5.3)	13.1 (4.2)	NS	NS	NS	NS
Frontal executive function	49.9 (6.9)	47.2 (7.8)	40.3 (12.3)	0.004	NS	0.055	0.005

Values are expressed as mean of composite scores (standard deviation). PD-H = Parkinson's disease with high CCSI score; PD-M = Parkinson's disease with middle CCSI score; PD-L = Parkinson's disease with low CCSI score; NS = not significant.

^a*P*-value from analyses of covariance.

^bBonferroni corrected *P*-values of the post hoc comparison test.

Figure 1.

Comparison of corticocortical functional connectivity with the PCC. Compared with normal controls, the PD-L patients showed decreased cortical functional connectivity in the primary motor and sensory areas, right frontal area, and posterior cortical areas (**A**). The PD-M patients showed decreased cortical functional connectivity in the right primary sensory area, right frontal area, and left precuneus (**B**). In a direct comparison, PD-L patients exhibited decreased cortical functional connectivity in the bilateral primary sensory areas and right parietal and frontal areas compared with the PD-H patients (**C**). PD-L patients had a similar pattern of decreased functional cortical connectivity with compared with the PD-M patients, however, the areas were less extensive (**D**). In a comparison of the PD-M and PD-H groups, PD-M patients had small clusters of decreased cortical connectivity in these areas relative to the PD-H groups (**E**). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the bilateral primary sensory areas and right frontal areas relative to the PD-H group (Fig. 1E). However, no areas where cortical functional connectivity was significantly

decreased in the PD-H or PD-M patients compared with the PD-L group were observed. The anatomical locations of the significant peaks based on seed region of interest in the posterior cingulate are listed in Table III.

Comparison of Resting State Striatocortical Functional Connectivity between PD-L, PD-M, and PD-H Patients

We used the caudate nucleus as a seed for the functional connectivity analysis, because the caudate is the key sub-cortical structure implicated in cognitive impairment in PD [Camicioli et al., 2009; Seibert et al., 2012]. The one sample *t*-test in the control and PD groups showed that brain regions including the bilateral frontal, temporal, occipital, and cerebellar areas have positive functional connectivity with the caudate. Compared with the controls, the PD-L patients showed increased positive striatocortical connectivity in the right frontal and left motor cortical areas and decreased connectivity in the right occipital area (Fig. 2A). The PD-M patients showed increased striatocortical connectivity in similar areas relative to the controls, however, these patients had decreased striatocortical connectivity in large areas of the occipital cortex (Fig. 2B). The PD-H patients exhibited decreased striatocortical functional connectivity in the bilateral occipital areas, right parietal area, and left primary motor area compared with the control subjects (Fig. 2C). In a direct comparison of the PD groups, in contrast to the patterns of cortical functional connectivity with the PCC, the PD-L patients exhibited increased striatocortical functional connectivity in the bilateral occipital and right frontal areas compared with the PD-H patients (Fig. 2D). The PD-L patients had a similar pattern of increased striatocortical functional cortical connectivity relative to the PD-M patients, however, the areas were less extensive than comparison between the PD-L and PD-H groups (Fig. 2E). In a comparison of PD-M and PD-H, the PD-M patients had increased striatocortical connectivity in the bilateral occipital areas, right precuneus, right frontal area, and left primary motor area compared with the patients with PD-H (Fig. 2F). However, no areas of significantly decreased cortical functional connectivity were observed in the PD-L patients compared with the PD-M or PD-H patients. The anatomical locations of the significant peaks based on seed region of interest in the caudate are listed in Table IV.

Correlation Analysis of Olfactory Performance and Resting State Functional Connectivity

In the voxel-wise correlation analysis, we found that the CCSI score was positively correlated with cortical functional connectivity with the PCC in the bilateral frontal and anterior cingulate, bilateral primary motor and sensory cortices, left temporal and parietal areas, and right cerebellum (Fig. 3A). Meanwhile, the cortical functional

TABLE III. Clusters displaying significantly different resting-state functional connectivity with seed region of interest in the posterior cingulate

Brain regions		Side	Stereotaxic coordinates (mm)			Maximum	Voxels
			x	y	z	t	
PD-L < Control	Precentral gyrus	R	+36	-22	+66	3.73	696
	Postcentral gyrus	R	+26	-50	+68	3.81	396
	Postcentral gyrus	L	-32	-36	+72	3.18	262
	Superior frontal gyrus	R	+12	-10	+78	4.03	124
	Supramarginal gyrus	R	+38	-46	+30	3.45	52
	Precuneus	L	-22	-58	+56	3.53	60
PD-M < Control	Postcentral gyrus	R	+40	-34	+62	3.01	136
	Middle Frontal gyrus	R	+34	+20	+50	-3.73	144
	Superior Frontal gyrus	R	+12	-10	+76	3.80	112
	Precuneus	L	-22	-58	+52	2.79	90
PD-L < PD-H	Postcentral gyrus extending into inferior parietal lobule	R	+52	-36	+66	3.84	738
	Postcentral gyrus extending into superior parietal lobule	L	-34	-34	+70	4.49	484
	Middle frontal gyrus	R	+22	-6	+56	4.00	254
	Superior frontal gyrus	R	+22	+16	+56	3.00	20
PD-L < PD-M	Supramarginal gyrus	R	+40	-50	+28	3.92	222
	Middle frontal gyrus	R	+26	+16	+52	3.48	173
	Precentral gyrus	R	+30	-26	+76	3.32	145
	Postcentral gyrus	R	+50	-28	+54	4.10	135
	Postcentral gyrus	L	-28	-36	+60	2.86	128
PD-M < PD-H	Postcentral gyrus	R	+50	-28	+32	3.75	229
	Superior parietal lobule	R	-60	-60	+72	3.16	216
	Superior frontal gyrus	R	-8	-8	+70	3.19	207
	Postcentral gyrus	L	+72	-36	+72	2.92	48
	Precentral gyrus	R	+64	-22	+64	2.74	30

PD-L = Parkinson's disease with low CCSI score; PD-M = Parkinson's disease with middle CCSI score; PD-H = Parkinson's disease with high CCSI score; R = right; L = left.

connectivity with the caudate was negatively correlated with the CCSI score in the right frontal areas, left primary motor area, bilateral occipital areas, precuneus, and right cerebellum (Fig. 3B). There were no significant clusters in which the CCSI score was negatively correlated with cortical functional connectivity with the PCC or positively correlated with cortical functional connectivity with the caudate. The anatomical locations of significant correlated with olfactory performance with seed region of interest in the PCC and caudate are listed in Table V. The conjunction analysis highlighted the bilateral primary sensory areas and right frontal areas as altered cortical functional networks with the PCC seed (Supporting Information Fig. S1 and Table S1). Additionally, this analysis revealed bilateral occipital areas and bilateral frontal areas as altered striatocortical functional networks with the caudate seed (Supporting Information Fig. S1 and Table S1).

DISCUSSION

The present study is the first to demonstrate that the patterns of resting state functional connectivity differ according to olfactory performance in nondemented

patients with PD. First, PD-L patients exhibited a significant attenuation of corticocortical functional connectivity in the bilateral primary sensory areas, right frontal areas, and right parietal areas compared to patients with PD-H or PD-M. Second, PD-L patients had significantly enhanced striatocortical functional connectivity in the bilateral occipital and right frontal areas compared to patients with PD-H or PD-M. Third, a correlation analysis revealed that olfactory performance was positively associated with cortical functional connectivity with the PCC, but negatively associated with cortical connectivity with the caudate. These data suggest that resting state functional connectivity might be closely associated with the state of olfactory performance in nondemented PD patients.

The primary olfactory cortex, including the piriform cortex, amygdala, and entorhinal cortex, plays a key role in processing olfactory information. In addition, higher brain areas such as the orbitofrontal and prefrontal areas, insular, striatum, precuneus, and cerebellum may also be involved in olfaction, depending on the olfactory performance task [Savic, 2002]. Thus, the task of odor identification is mediated by sensory processing, as well as higher cortical functions involving especially semantic circuits. In

terms of the interplay between cognition and olfactory performance, the deterioration of verbal and nonverbal memory function, slower processing speed, and impaired language performance may influence odor identification in patients with PD [Damholdt et al., 2011; Hudry et al., 2003]. In agreement with previous findings, this study found that PD-H patients tended to exhibit better cognitive performance in visuospatial, language, and frontal executive function tasks relative to PD-L patients. Regarding the neural correlates encompassing olfactory performance and cognition, several metabolic or structural candidates have

been suggested in healthy controls or patients with PD. For example, several studies have demonstrated that decreased gray and white matter densities in the limbic and orbitofrontal areas are associated with olfactory impairment in the elderly or PD patients [Bitter et al., 2010; Ibarretxe-Bilbao et al., 2010]. Additionally, decreased cerebral metabolism in the piriform cortex and amygdala is associated with olfactory dysfunction in patients with PD [Baba et al., 2011]. Moreover, decreases in the dopaminergic and cholinergic innervation of temporolimbic areas are thought to be responsible for olfactory identification that is related to cognitive performance [Bohnen et al., 2008, 2010]. Accordingly, the temporolimbic areas and frontal cortex appear to be key metabolic or anatomical correlates of olfactory performance, which might shed light on the relationship between olfactory impairment and cognitive dysfunction.

The PCC is a central region in the DMN, and exhibits significant functional connectivities with cortical areas such as the medial prefrontal, dorsolateral prefrontal, inferior parietal, and temporal cortices [Greicius et al., 2003]. Thus, functional connectivity with the PCC is closely associated with mental processes such as memory encoding, retrieval tasks, and/or visuospatial orientation. A recent fMRI analysis found that there is a disruption of the resting state functional connectivity in the temporal and parietal areas within the DMN during the early stages of PD. Such altered connectivity occurs prior to any observable clinical evidence of cognitive impairment and is significantly correlated with cognitive parameters such as memory and visuospatial performance [Tessitore et al., 2012]. It has also been suggested that cortical functional connectivity with the PCC exhibits distinctive patterns according to cognitive status. PD patients with dementia display a significantly decreased functional connectivity in the prefrontal areas relative to cognitively normal PD patients and

Figure 2.

Comparison of striatocortical functional connectivity with the caudate nucleus. Functional connectivity in patients with PD was compared with that of control subjects. The PD-L (A) or PD-M (B) patients showed increased striatocortical connectivity in the right frontal and left primary motor areas (blue color) and decreased connectivity in the right occipital area (yellow color). The PD-H patients exhibited decreased striatocortical functional connectivity in the occipitoparietal areas and left primary motor area (C). In a direct comparison, the PD-L patients exhibited increased striatocortical functional connectivity in the bilateral occipital areas and right frontal areas compared with the PD-H (D) or PD-M patients (E). In a comparison of PD-M and PD-H, the PD-M patients showed increased striatocortical connectivity in the bilateral occipital areas, right precuneus, right frontal area, and left primary motor area compared with the patients with PD-H (F). Brown color: the former group > the latter group, blue color: the former group < the latter group. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE IV. Clusters displaying significantly different resting-state functional connectivity with seed region of interest in the caudate

	Brain regions	Side	Stereotaxic coordinates (mm)			Maximum	Voxels
			x	y	z	t	
Control < PD-L	Superior frontal gyrus	R	+14	+60	-6	-4.19	245
	Precentral lobule	L	-8	-46	+58	-2.96	59
	Precentral gyrus	L	-40	-10	+60	-2.96	39
Control > PD-L	Middle occipital gyrus	R	+46	-80	+6	2.56	7
Control < PD-M	Superior frontal gyrus	R	12	+62	-6	-4.47	221
	Paracentral lobule	L	-22	-44	-62	-2.94	60
Control > PD-M	Inferior occipital gyrus	R	+52	-80	-6	2.84	175
	Middle occipital gyrus	R	+46	-6	+8	-2.39	9
Control > PD-H	Middle occipital gyrus	R	+40	-98	-4	3.62	338
	Superior parietal lobule	R	+4	-72	+60	3.70	199
	Precentral gyrus	L	-40	-22	+60	3.26	172
	Inferior occipital gyrus	L	-26	-88	-14	3.15	147
	Precuneus	L	-12	-50	+56	-4.14	372
PD-H < PD-L	Precentral gyrus	L	-38	-14	+62	-4.13	325
	Middle occipital gyrus	R	-68	-68	-18	-4.17	209
	Lingual gyrus	L	-90	-90	-12	-3.75	192
	Medial frontal gyrus	R	+50	+50	-14	-3.74	184
	Middle occipital gyrus	R	+58	-72	-18	-3.27	143
PD-M < PD-L	Precuneus	L	-12	-50	+56	-2.83	28
	Precentral gyrus	L	-40	-12	+62	-2.43	20
	Precentral gyrus	L	-34	-14	+60	3.68	289
PD-M > PD-H	Precuneus	R	0	-70	+54	2.94	200
	Middle occipital gyrus	R	+34	-88	-2	3.06	102
	Medial frontal gyrus	R	+4	+52	-18	3.18	39
	Lingual gyrus	L	-14	-90	-14	3.50	123

PD-L = Parkinson's disease with low CCSI score; PD-M = Parkinson's disease with middle CCSI score; PD-H = Parkinson's disease with high CCSI score; R = right; L = left.

healthy controls [Rektorova et al., 2012; Seibert et al., 2012], although one of these studies showed different patterns of functional connectivity, using only at a very liberal threshold. In the present study, there was a significant decrease in functional connectivity with the PCC in patients with either PD-L or PD-M compared to healthy

controls; however, disrupted functional connectivity with the PCC was relatively more extensive in the PD-L patients than the PD-H patients. A direct comparison of the groups revealed that PD-L patients had decreased cortical functional connectivity in the bilateral primary sensory areas and right frontal and parietal areas compared to PD-

Figure 3.

Correlation analysis of olfactory performance and resting state functional connectivity. In general, olfactory performance was positively associated with cortical functional connectivity with the posterior cingulate (A), but negatively associated with cortical connectivity with the caudate (B). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE V. Clusters displaying significant resting-state functional connectivity correlated with olfactory performance with seed region of interest in the posterior cingulate and caudate

Seed	Brain regions	Side	Stereotaxic coordinates (mm)			Maximum	Voxels
			<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	
Posterior cingulate	Postcentral gyrus	L	−50	+36	+68	4.01	2130
	Postcentral gyrus	R	+44	+26	+32	4.07	1392
	Precentral gyrus	L	−28	+34	+60	3.89	1051
	Precentral gyrus	R	+30	+20	+82	3.75	225
	Middle frontal gyrus	L	−30	+4	+58	3.72	442
	Middle frontal gyrus	R	+20	+4	+62	3.80	402
	Inferior parietal Lobule	L	−50	+28	+22	3.55	260
	Anterior cingulate	L	−4	−22	+20	4.63	259
	Parahippocampal gyrus	L	−26	−56	+2	3.26	319
	Cerebellum	R	+38	−46	−26	5.53	449
Caudate	Medial frontal gyrus	R	+6	+50	−14	−4.27	780
	Inferior occipital gyrus	L	−40	−92	−18	−4.23	748
	Precuneus	L	−12	−50	+56	−4.20	446
	Precentral gyrus	L	−38	−18	+60	−3.97	505
	Middle occipital gyrus	R	+58	−70	−18	−3.99	329
	Superior frontal gyrus	R	+4	−6	+70	−3.53	255
	Cerebellum	R	+36	−70	−56	−4.17	283

PD-L = Parkinson's disease with low CCSI score; PD-M = Parkinson's disease with middle CCSI score; PD-H = Parkinson's disease with high CCSI score; R = right; L = left.

H or PD-M patients. Furthermore, a correlation analysis demonstrated that the olfactory performance was positively correlated with cortical functional connectivity with the PCC in similar areas, which further supports the existence of a positive relationship between olfactory performance and cortical functional connectivity with the PCC. Accordingly, the present analyses of functional connectivity provide evidence that PD-L patients have disrupted cortical connectivity with the PCC in the early stages of the disease prior to the clinical manifestation of dementia. This might explain why olfactory performance is closely associated with the underlying cognitive dysfunction in nondemented PD patients.

Interestingly, the decreased functional connectivity with the PCC in PD-L patients relative to PD-H patients was not restricted to the limbic area, a key structure in olfactory identification, but was rather extensively associated with the frontal and temporoparietal areas. According to a recent longitudinal study, olfactory performance is closely related to visuoperceptual and memory functions and processing speed in addition to general cognition, and more importantly, severe hyposmia at baseline is the most important indicator of the risk for developing dementia in PD [Baba et al., 2012]. Therefore, the disrupted functional connectivity within extensive cortical regions observed in PD-L patients may imply that the olfactory performance of nondemented patients with PD closely reflects their general cognitive status across specific cognitive domains. Furthermore, it might indicate that olfactory dysfunction may act as a prognostic marker for ongoing cognitive decline in PD.

Several studies have demonstrated that corticostriatal functional connectivity follows the anatomy of the corticostriatal loops [Kelly et al., 2009; Postuma and Dagher, 2006]. The caudate nucleus is also functionally connected to large parts of the prefrontal cortex, as well as the parietal, temporal, and cerebellar cortices, and plays a role in the discrimination of odor quality [Savic et al., 2000]. Unexpectedly, RSN analysis with the caudate seed in the present study revealed that, in contrast to the patterns of cortical functional connectivity with the PCC, PD-L patients had significantly increased cortical functional connectivity mainly in the bilateral occipital and right frontal areas compared to PD-M or PD-L patients. This pattern was consistently identified in the correlation analyses, which demonstrates that cortical functional connectivity with the caudate is negatively correlated with olfactory performance in the left temporoparietal cortices and right occipital area in addition to the frontal and cerebellar areas. Although it is difficult to explain the RSN result for the caudate in detail, we speculate that the enhanced functional connectivity in PD-L patients is a secondary compensation effect by PD-L patients to maintain olfactory performance. However, a longitudinal study of serial changes in olfactory performance-associated RSN patterns is needed to resolve this issue.

In a previous voxel-based volumetric analysis, we found that although the cognitive performance of PD patients with higher levels of olfactory performance is better, the cortical atrophy in areas related to olfaction is more severe in these patients than in patients with lower olfactory performance [Lee et al., 2014]. We also found that the

olfactory performance in patients with PD was negatively correlated with the gray matter and intracerebral volumes. As regional cortical atrophy greatly influences the resting state functional connectivity, the cortical thickness of the PD-L and PD-H patients in this study was adjusted to avoid atrophy-related functional connectivity. Therefore, it is noteworthy that the olfactory performance-related RSN patterns observed in this study might be independent of significant regional cortical atrophy in nondemented PD patients.

The strengths and limitations of this study need to be addressed. The present research included drug-naïve de novo patients with PD to exclude the effects of antiparkinsonian medications on functional connectivity. However, the number of study subjects was too small to draw firm conclusions. In addition, we could not completely exclude patients with parkinsonian plus syndrome among PD-H patients, because the follow-up period was relatively short and we have no pathology data. Consequently, our results should be interpreted cautiously. Finally, although this study included important cortical and subcortical seeds responsible for cognition in PD, these seeds could not represent complete functional connectivity analysis. Therefore, a further study using other cortical and subcortical seeds or other imaging analytic tools, such as independent component analysis, is needed to elucidate functional network maps.

CONCLUSIONS

We demonstrated that resting state corticocortical or striatocortical functional connectivity exhibits a distinctive pattern depending on olfactory performance. These data might shed light on a meaningful relationship between olfactory impairment and cognitive dysfunction in nondemented patients with PD.

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