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ORIGINAL ARTICLE

Association of olfaction dysfunction with brain microstructure in prodromal Parkinson disease

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Abstract

Objective Although olfaction dysfunction is now considered as an established clinical marker of prodromal Parkinson disease (PD), little is known about the neural underpinnings of olfaction dysfunction in the prodromal phase of PD. The aim of this study was to examine the microstructural association of olfaction in prodromal PD compared to early stage drug-naïve PD patients.

Methods Diffusion MRI connectometry was conducted on 18 early PD and 17 prodromal PD patients to investigate the differences in group in terms of altered connectivity, i.e., integrity of white matter tracts, and subsequently to study the correlation of University of Pennsylvania Smell Identification Test (UPSIT) score to white matter integrity in each group using a multiple regression model considering age, sex, RBD, and MoCA, as covariates.

Results Individuals with prodromal PD had significantly higher quantitative anisotropy (QA) comparing with PD patients in bilateral middle cerebellar peduncles and right arcuate fasciculus. Multiple regression analysis in prodromal PD demonstrated positive association between UPSIT score and connectivity in left and right subgenual cingulum, right inferior fronto-occipital fasciculus, left corticospinal tract, left parietopontine, left corticothalamic tract, and the body and the splenium of corpus callosum.

Conclusion These results indicate that PD and prodromal PD patients, which were matched for sex, UPSIT, and MoCA scores, have different white matter fiber architecture. Thus, it is postulated that olfaction dysfunction in prodromal and early clinical phases of PD may involve distinct pathogenesis. Increased network connectivity in prodromal and early PD may suggest the neural compensation.

Keywords Prodromal PD · Olfaction · UPSIT · Diffusion MRI · Parkinson disease

Introduction

Parkinson's disease (PD) is a degenerative disorder of the nervous system commonly recognized with motor complications, including resting tremor, rigidity, and bradykinesia, which is neuropathologically due to α-synuclein-mediated dopaminergic depletion in the substantia nigra pars compacta (SNpc) [1]. In addition to nigral disruption, extranigral pathways and structures are disturbed in PD leading to various non-motor symptoms (NMS) and heterogeneous clinical manifestations. Although PD is well-known for its motor impairments, NMS, such as rapid eye movement sleep behavior disorder (RBD), depression, apathy, and olfaction dysfunction have recently been shown to be of considerable importance in PD. Based on movement disorder society criteria, PD consists of three distinct stages as preclinical, prodromal, and clinical PD [2–4]. Prodromal PD is when signs and symptoms are present, but they are inadequate to make the diagnosis of PD [5, 6]. Prodromal PD is chiefly characterized by non-motor symptoms such as hyposmia/anosmia, RBD, constipation, depression, and orthostatic hypotension [7], most of which are interestingly related to the peripheral nervous system. Of these non-motor symptoms, impairment of olfaction as a result of olfactory bulb disruption has recently been attracting remarkable attention. More than 80% of PD patients have hyposmia, which is higher than the prevalence of most of other NMS, and therefore olfaction dysfunction serves as the most sensitive PD marker [8]. According to the stages of Braak system, α-synuclein deposition occurs primarily in the olfactory nucleus; thereafter, it spreads to other regions of the brain and only affects SN in the third stage [9].

Human sense of smell gives the ability to detect and distinguish different odors in the environment, e.g., fragrance of people, foods, etc. Olfaction is evolutionary essential as it

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notifies people of the smell of perilous objects like decayed food [10, 11]. Olfactory dysfunction has been proved to be in association with multiple neurodegenerative diseases, mostly with PD. Strong evidence of multiple longitudinal studies proves that olfactory loss precedes PD [12–18] and is now considered as an established clinical marker of prodromal PD [19]. Despite the very simple way of olfaction assessment, it is almost always ignored in the clinical practice [20]. Assessment of olfactory function may help to fathom the pathogenesis of PD and due to the high and early incidence of olfactory dysfunction; the evaluation of this symptom is proposed to be of significant value in the diagnosis of PD [21, 22]. It is postulated that olfactory dysfunction is correlated with PD progression. Furthermore, the levels of olfactory impairment in specific PD subtypes are various [23]. University of Pennsylvania Smell Identification Test (UPSIT) [24] is a simple and widespread non-invasive tool for the assessment of olfaction, which can be utilized in both research and clinical methods. Within this test, a predefined set of odorants are introduced to the patient in a multiple-choice setting.

Neuroimaging studies applying single-photon emission computed tomography (SPECT) or positron emission tomography (PET) have demonstrated that olfactory impairment is associated with metabolic disruptions in different brain areas, such as limbic, occipital, and striatal regions [25–31]. Moreover, functional MRI (fMRI) methods have detected abnormal neuronal activity in some brain areas and also decreased connectivity between various regions, possibly contributing to olfactory impairment. In more details, it is documented that there is depressed activity in bilateral rectus, orbitofrontal cortex (OFC), amygdala, and parahippocampus in hyposmic PD patients [32].

Diffusion magnetic resonance imaging (DMRI) is a quite novel method, which has promoted our understanding of white matter (WM) microstructure alterations in pathological states such as PD. This method is based on the diffusion of water molecules and depending on the direction of diffusion restriction; the structure of local tissues can be estimated.

In this context, connectometry is a novel approach constituting statistical analysis of diffusion MRI signals that simply tracks the WM tracts, which are significantly different between groups, or traces WM fibers exhibiting significant association with a variable of interest. Connectometry extracts the spin distribution function (SDF) in a given fiber orientation, as a measure of water density along that direction. There are a multitude of diffusion indices derived from spin density, i.e., SDF, quantitive anisotropy (QA) being one of them [33]. QA in each fiber tract represents the peak density of water diffusion along the main direction of WM fibers. Unlike conventional diffusion tensor imaging, DMRI connectometry is concerned with the density of water diffusion, not just the direction of water diffusion, i.e., how fast the molecules diffuses in different directions. The use of QA in DMRI provides further spatial resolution to identify tracts in regions with kissing or crossing tracts, for instance, in long associational tracts, projecting to or originating from the temporal lobe. In this regard, decreased type 1 error, higher spatial resolution, and lower susceptibility to partial volume effect are the main privileges of QA in DMRI connectometry compared to measures from conventional diffusion tensor imaging (DTI) [34–37].

DMRI studies of PD patients employing region of interest (ROI) analysis have demonstrated that in addition to the primary olfactory cortex, olfactory-associated degeneration had encroached upon OFC, temporal, parietal-occipital, and cingulate cortices [25, 38–40].

Parkinson's progression marker initiative (PPMI) is a comprehensive multicenter prospective study providing valuable data regarding different aspects of PD patients, such as demographic, imaging, serum and cerebrospinal fluid (CSF) biomarkers, and neuropsychological data [41]. In this study, using PPMI database, the association between olfactory dysfunction and connectometry patterns was investigated. In fact, we compared UPSIT-matched PD and prodromal PD groups based on connectometry patterns and sought the fibers that have distinctive WM QA based on MRI findings. Successively, it was investigated whether the degree of olfactory impairment (UPSIT score) can predict the microstructural abnormalities, as shown by QA, in the brain of PD or prodromal PD patients.

Materials and methods

Participants

Participants involved in this research were recruited from PPMI (http://www.ppmi-info.org/). The study was approved by the institutional review board of all participating sites in the Europe, including Attikon University Hospital (Greece), Hospital Clinic de Barcelona and Hospital Universitario Donostia (Spain), Innsbruck University (Austria), Paracelsus-Elena Clinic Kassel/University of Marburg (Germany), Imperial College London (UK), Pitié-Salpêtrière Hospital (France), University of Salerno (Italy), and in the USA, including Emory University, Johns Hopkins University, University of Alabama at Birmingham, PD and Movement Disorders Center of Boca Raton, Boston University, Northwestern University, University of Cincinnati, Cleveland Clinic Foundation, Baylor College of Medicine, Institute for Neurodegenerative Disorders, Columbia University Medical Center, Beth Israel Medical Center, University of Pennsylvania, Oregon Health & Science University, University of Rochester, University of California at San Diego, and University of California, San Francisco. Written informed consent was obtained from all participants before study enrolment. The study was performed in accordance with relevant guidelines and regulations [42]. These participants were tested and confirmed negative for any neurological disorders apart from

PD. The participants' PD status was confirmed by Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), and the loss of dopaminergic neurons was observed on DAT scans. MDS-UPDRS was applied to confirm PD status of enrolled participants. Subjects were only excluded if imaging failed specific quality control criteria.

Participants with prodromal PD should had aged 60 and above and had confirmation from olfactory core that olfaction as determined by UPSIT is at or below the 10th percentile by age and gender, or confirmation from sleep core that subject's polysomnography (PSG) meets criteria for RBD. All prodromal PD patients were without other neurological and psychiatric conditions and the majority of them also showed DAT deficits similar to subjects with early PD (mild to moderate DAT deficit).

Only PD participants who met the following additional criteria were included in the current study: (1) PD with anosmia and hyposmia (UPSIT < 24) and (2) no diagnosis of dementia and Montreal Cognitive Assessment (MoCA) scores > 22.

Finally, a total of 18 PD patients and 17 prodromal PD were recruited from available diffusion tensor imaging (DTI) baseline data from PPMI project.

Participants in each category were matched by sex, UPSIT, and MoCA (Table 1).

Data acquisition

Data used in the preparation of this article were obtained from the PPMI database (www.ppmiinfo.org/data) [42]. This dataset was acquired on a three Tesla Siemens scanner, producing 64 diffusion MRI (repetition time = 7748 MS, echo time = 86 ms; voxel size: 2.0 × 2.0 × 2.0 mm3; field of view = 224 × 224 mm) at $b = 1000$ s/mm2 and one b0 image along with a 3D T1-weighted structural scan (repetition time = 8.2 ms, echo time = 3.7 ms; flip angle = 8°, voxel size: 1.0 × 1.0 × 1.0 mm^3; field of view = 240 mm, acquisition matrix = 240 × 240).

Diffusion MRI processing

The diffusion MRI data were corrected for subject motion, eddy current distortions, and susceptibility artifacts due to the magnetic field inhomogeneity using Explore DTI toolbox [34].

Connectometry: between-group analysis

The diffusion data were reconstructed in the MNI space using q-space diffeomorphic reconstruction (QSDR) to obtain the spin distribution function (SDF) [43].

In the first step of our analyses, we used diffusion MRI connectometry to identify WM tracts in which QA was significantly different between two groups. Resulting uncorrected output was corrected for multiple comparisons by false discovery rate (FDR). A deterministic fiber tracking algorithm was conducted along the core pathway of the fiber bundle to connect the selected local connectomes [44]. Tracts with QA > 0.1, angle threshold lesser than 40° and tract length greater than 40 mm were included. To estimate the false discovery rate, a total of 2000 randomized permutations were applied to the group label to obtain the null distribution of the tract length. Permutation testing allows for estimating and correcting the false discovery rate (FDR) of type I error inflation due to multiple comparisons.

Connectometry: multiple regression analysis

Diffusion MRI connectometry was used to study the effect of UPSIT in PD and prodromal PD. A multiple regression model was used to investigate correlation of UPSIT score with WM QA, considering age, sex, RBD, and MoCA, as covariates in the model. The SDF was normalized. A T score threshold of 2.5 was assigned to select local connectomes, and the local connectomes were tracked using a deterministic fiber tracking

Table 1 Demographic and clinical characteristics of the PD and PD prodromal

Measure	PD			PD prodromal			PD—PD prodromal	
							Group difference	
	n	Mean	Range	*n*	Mean	Range	*t* value	*p* value
Age (years)	18	62.88 (6.2)	52–82	17	67.05 (5.3)	61–82	− 2.121	0.042
Sex (m/f)	18	12/6		17	15/2			0.228[a]
UPDRS 3	18	26.83 (8.1)	14–41	0				
H&Y	18	1.66 (0.4)	1–2	0				
UPSIT	18	14.5 (5.6)	5–24	17	13.82 (4.9)	8–22	0.379	0.707
RBD	18	4.77 (3.4)	0–12	17	9.52) 4.2)	2–14	− 3.621	0.001
MoCA	18	27.66 (1.9)	24–30	17	27.29 (1.8)	23–30	0.584	0.563

H&Y Hoehn and Yahr, *MoCA* Montreal Cognitive Assessment, *PD* Parkinson's disease, *RBD* REM sleep behavior disorder, *UPDRS3* Unified Parkinson's disease rating scale Part III, *SD* standard deviation

[a] Chi-square tests

algorithm. A length threshold of 40 mm was used to select tracks. The seeding density was 50 seeds per mm^3. To estimate the false discovery rate, a total of 2000 randomized permutation were applied to the group label to obtain the null distribution of the track length. The analysis was conducted using publicly available software DSI Studio (http://dsi-studio.labsolver.org).

Results

Demographics

Demographic and clinical features of PD patients and Prodromal PD individuals are depicted in Table 1. Eighteen PD patients and 17 prodromal PDs were included in this study. Male to female ratio for PDs and prodromal PDs was 12/6 and 15/2, respectively. Prodromal PD patients were slightly older than PD patients (mean age = 67.05 and 62.88 respectively, p value = 0.042). Prodromal PDs and PDs were not significantly different in UPSIT score (p value = 0.707), meaning that the two group were matched for olfaction. Nonetheless, there was a significant difference in RBD scores comparing two groups of participants (p value = 0.001).

Between-group analysis

PD patients and individuals in prodromal phase of PD were matched in terms of sex, UPSIT, and MoCA score. Individuals with prodromal PD had significantly higher QA comparing with PD patients in two of the WM fibers (Fig. 1): bilateral middle cerebellar peduncles and right arcuate fasciculus (FDR = 0.00109567) (Table 2). On the other hand, the following fibers had higher QA in individuals with PD in comparison to prodromal PD patients: left inferior longitudinal fasciculus, left fronto-occipital fasciculus, right and left fornix, right corticospinal tract, and right and left cingulum (FDR = 0.00147565) (Table 2).

Multiple regression analysis

Multiple regression analysis was carried out to search for QA alterations of WM fibers in correlation with UPSIT score.

More specifically in prodromal PD patients, the connectometry analysis identified QA of left and right subgenual cingulum, right inferior fronto-occipital fasciculus, left corticospinal tract, left parietopontine tract, left corticothalamic tract, and body and splenium of corpus callosum to have positive correlation with UPSIT score (FDR = 0.0298507) (Table 3), but it did not find negative correlation between QA in any of WM fibers and UPSIT score.

In PD patients, the connectometry analysis identified QA of left and right subgenual cingulum, left and right inferior fronto-occipital fasciculus, and left corticospinal tract to have positive association with UPSIT score (FDR < 0.001). In contrast, bilateral middle cerebellar peduncle, right uncinate fasciculus, left inferior longitudinal fasciculus, body and genu of corpus callosum, and right posterior cingulum QA were negatively associated with UPSIT score (FDR < 0.001) (Table 3).

Discussion

In the present study, we investigated the possible association between the olfaction impairment and microstructure of WM fibers in the brains of individuals with PD and patients in prodromal phase of PD. To the best of our knowledge, this is the first study to seek for underlying microstructural alternations in UPSIT-matched PD and prodromal PD patients.

For this purpose, DMRI connectometry was employed in order to find WM fibers with altered connectivity in PD and prodromal PD individuals with similar levels of olfactory impairment. Also, microstructural changes in WM fibers associated with olfaction dysfunction in both PD and prodromal PD groups were analyzed using connectometry. To be more precise, our analysis indicated that middle cerebellar peduncle and right arcuate fasciculus had more WM integrity in prodromal PD patients. Just in contrast, it was demonstrated that multiple fibers, including left inferior longitudinal fasciculus, left fronto-occipital fasciculus, right and left fornix, right and left corticospinal tract, right and left cingulum, and right and left middle cerebellar peduncle had higher QA in PD patients. These findings lead to proposal of two hypotheses; first and foremost, it is assumed that olfactory dysfunction in prodromal PDs and individuals with PD are probably due to divergent underlying pathologic mechanisms, since these two groups were matched in terms of sex, and UPSIT score, but still show different connectivity patterns. Some of these tracts have been previously indicated in the olfactory dysfunction in PD. The cingulum network mainly consisting of parahippocampal, septal, and entorhinal gyri is responsible for the linkage between cingulate, prefrontal, and temporal cortical regions [45]. It has been shown that anterior cingulum is atrophied in initial stages of disease [46]. Also in the bargain, related neuroimaging data have indicated that anosmic PD patients relative to HCs, show elevated FA in WM adjacent to entorhinal cortical area, which is assumed to be cingulum tract. Thus, it is proposed that alternations in the connectivity of cingulum at least partly account for mild impairment in smell identification in early PDs. The fornix, whose alternation is an essential biomarker of depression in PD, is the connecting WM fiber in the limbic circuit [47, 48]. In contrast, a recent study showed that integrity of fornix, as a limbic connection, could not differentiate PD patients with different degrees of olfactory impairment [49]. In addition, in the similar study, bilateral corticospinal tract and middle cerebellar peduncles exhibited significantly different connectivity in

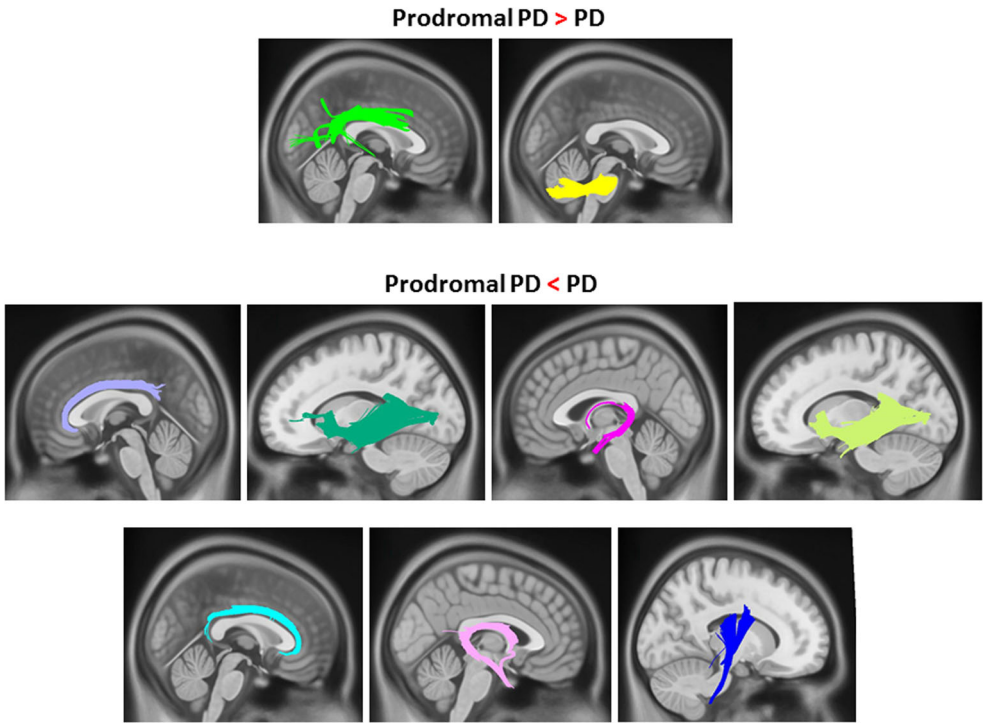

Fig. 1 White matter pathways with significantly reduced anisotropy in PD patients compared to PD prodromal (FDR = 0.00109567). **a** Right arcuate fasciculus, **b** middle cerebellar peduncle, and white matter pathways with significantly increased anisotropy in PD patients compared to PD prodromal (FDR = 0.00147565), **c** left cingulum, **d** left inferior fronto-occipital fasciculus, **e** left fornix, **f** left inferior longitudinal fasciculus, **g** right cingulum, **h** right fornix, **i** right corticospinal tract

PD patients with severe olfactory dysfunction and patients with moderate microsmia or otherwise normal olfaction [49].

Secondly, as it is clear, individuals with PD are in a more progressed stage of disease than prodromal PDs, which are in the initial stages of disease. Notwithstanding, the results exhibited that fibers with higher connectivity in PD participants considerably outnumber fibers with higher connectivity in prodromal PDs, i.e., the overall connectome connectivity is stronger in participants with more severe disease progression. Also, a previous study using graph-theoretical analysis suggested that compared to de novo PD patients and HCs, individuals with prodromal PD presented with an increased local connectivity between several areas, which are responsible for controlling motor function, sleep regulation, and olfactory sensation [50]. They further showed that in comparison to HCs, de novo PD patients had decreased connectivity within prefrontal areas. Our outcomes from DMRI survey are, in some way, incompatible with these results. This phenomenon can partly be attributed to compensatory mechanisms occurring with disease progression. In addition, the variations in the study population, i.e., we included olfactory-impaired PDs and prodromal PDs, different stages of disease progression, and also different methods of imaging analysis may explain these discrepancies.

Some recent studies using graph-theoretical methods reported that de novo PD patients display slightly diminished subnetwork connectivity in WM fibers connecting bilateral supplementary motor areas (SMAs) and temporal, frontal, and occipital lobes with no considerable changes in global network, implying local degeneration in initial stages of PD [50–52].

Subsequently, we sought for possible association between WM connectivity (QA) and olfactory impairment (UPSIT score) in PD patients and prodromal PDs. The results of multiple regression models in prodromal PDs, illustrated that there is a significant positive association between UPSIT score and the augmented connectivity of left and right subgenual cingulum, right inferior fronto-occipital fasciculus, left corticospinal tract, left parietopontine, left corticothalamic, and body and splenium of corpus callosum. Furthermore, in individuals with PD, we demonstrated that there is a negative correlation between left and right subgenual cingulum, left and right inferior fronto-occipital fasciculus, and left corticospinal tract. In contrast, we found bilateral middle cerebellar peduncle, right uncinate fasciculus, left inferior longitudinal fasciculus, body and genu of corpus callosum, and right posterior cingulum with positive association with UPSIT score in PD patients.

Recently, it was demonstrated that compared to HCs, the connectivity between parahippocampus and cerebellum and also between the SMA and putamen is increased in prodromal

Table 2 Regions with significantly different connectivity in between group comparing of PD patients with prodromal PD

PD > prodromal PD (FDR = 0.00147565)	PD < prodromal PD FDR = 0.00109567)
Left inferior longitudinal fasciculus	Middle cerebellar peduncle
Left and right fornix	Right arcuate fasciculus
Left inferior fronto-occipital fasciculus	
Left and right corticospinal tract	
Left and right cingulum	

Table 3 Fibers with significantly association with UPSIT in PD patients and prodromal PD

Fibers with positive association with UPSIT in PD (FDR < 0.001)	Fibers with negative association with UPSIT in PD (FDR < 0.001)
Left and right subgenual cingulum	Right posterior cingulum
Left and right inferior fronto-occipital fasciculus	Middle cerebellar peduncle
Left corticospinal tract	Right uncinated fasciculus
	Left inferior longitudinal fasciculus
	Body and genu of corpus callosum
Fibers with positive association with UPSIT in prodromal PD (FDR = 0.0298507)	
Right superior cerebellar peduncle	
Right and left subgenual cingulum	
Right inferior fronto-occipital fasciculus	
Left corticospinal tract	
Left parietopontine	
Left corticothalamic	
Body and splenium of corpus callosum	

PDs [50]. The parahippocampus is known to be involved in olfaction and sleep regulation, as it is a component of thalamocortical network [53–55]. Correspondingly, comparing prodromal PDs with PD patients, fibers connecting areas governing olfaction and sleep activities had elevated connectivity in prodromal PDs [54, 56].

Previous structural and functional studies have found that PD patients with olfactory dysfunction are presented with reduced FA in the rectus and decreased function and connectivity in the OFC and rectus [32, 57, 58]. Some fMRI studies have exhibited that immense changes occur in the functional connectivity in the brain of olfactory-impaired PDs [32, 55, 59]. Paradoxically, there are studies not observing such widespread changes but rather alterations only in the microstructure of a single network [58]. A recent study reported that relative to structural alternations, functional changes are highly more noticeable in de novo PD. Supporting this notion, neuroimaging surveys in PD patients with hyposmia elucidated that studies employing functional imaging, such as PET and SPECT, possess greater power and potential to detect olfactory-related alternations rather than structural methods [58]. Thus, it is predictable that our structural study detects less olfactory-related changes compared to functional or metabolic imagings. Additionally, various methods for imaging analysis may be responsible for inconsistency in prior findings. Connectometry is considered a highly sensitive method for capturing association of even segments of WM tracts with a variable of interest, while other DTI analysis methods like TBSS or ROI analysis average between all fibers of a specified fiber tract, making them amenable to missing the true association of that WM tract with study variables. In addition, connectometry analysis instead of FA applies QA as a measure of anisotropy and WM integrity which unlike FA, it shows the peak density of water diffusion rather than diffusion velocity and is more sensitive to axonal damage in neurological disorders. One of the limitations of this study is the small number of participants and the reason for this issue is that we only investigated PD and prodromal PD individuals, with relatively low score on UPSIT, i.e., they were matched based on UPSIT score as well as for sex and MoCA.

On the whole, it can be postulated that limbic white matter, corticospinal, occipitotemporal, and inferior frontotemporal pathways are disrupted in prodromal phases of PD and derangement of quite the same pathways are responsible for olfaction dysfunction in prodromal PD. It implies that olfaction dysfunction, as the main neurological entity in prodromal PD, is tightly concreted with the main structural abnormalities in this phase, i.e., small-world network formation. On the other hand, superior frontotemporal and cerebellar pathways were shown to be mainly perturbed in clinical phases of PD. Interestingly, olfaction dysfunction in this group was strongly associated with higher QA in some WM tracts and lower QA in some other WM tracts, which was mainly attributed to compensatory mechanisms and formation of small networks. In fact, it can be hypothesized that along with disease progression, the compensatory mechanisms alter the structural architecture of brain. Another theory is that emergence of diverse clinical symptoms other than olfaction could partially make changes to these networks. Thus, this study suggests that the olfaction dysfunction in prodromal phase of PD and in clinical PD involve distinct pathomechanisms, which are not merely associated with olfaction dysfunction. On this way, the confounding role of other preclinical manifestations of PD such as REM sleep behavior disorder (RBD) in structural differences between prodromal and overt clinical PD needs to be further investigated in future.

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Authors' contributions H.S.M, M.H.A. contributed to the conception and design of the study; M.H.A. contributed to data collection and analysis; and H.S.M, M.D, and E.S.D contributed to writing and revising the manuscript.

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Compliance with ethical standards

Ethical approval All procedures performed here, including human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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