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Aberrant corticospinal tract characteristics in prodromal PD: A diffusion tensor imaging study

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ABSTRACT

Introduction: Parkinson's disease (PD) is typically diagnosed when motor symptoms first occur. However, PD-related non-motor symptoms may appear several years before diagnosis. REM sleep behaviour disorder (RBD) and olfactory deficits (hyposmia) are risk factors, but they are not specific for predicting progression towards PD. Other PD-related markers, for example brain imaging markers, may help to identify preclinical PD in hyposmic RBD patients. Studies have reported abnormal structural characteristics in the corticospinal tract (CST) of PD patients, but it is unclear whether hyposmic RBD patients have similar abnormalities that may help to predict PD in these individuals. This study examined whether CST abnormalities may be a potential marker of PD risk by using diffusion tensor imaging (DTI) measures.

Methods: Twenty hyposmic RBD patients, 31 PD patients, and 29 healthy controls (HCs) were studied. DTI data were collected on a 1.5 T MRI scanner and CST characteristics (FA, MD, AD, and RD) were evaluated using probabilistic tractography (with seed regions in the bilateral primary motor cortex and mediolateral cerebral peduncles). Olfactory function was assessed with the University of Pennsylvania Smell Identification Test (UPSIT).

Results: Hyposmic RBD patients showed significantly higher mean diffusivity (MD) values of the right CST compared to HCs but did not differ from PD patients. PD patients showed a trend of higher MD values compared to HCs.

Conclusions: Altered diffusivity in the CST seems to be associated with RBD. The combination of RBD, hyposmia, and CST alterations may be related to later development of PD with comorbid RBD.

Parkinson's disease (PD) is the second most common neurodegenerative disease with a prevalence of approximately-one percent in the population over 60 years of age [1]. Typically, PD is clinically diagnosed with the appearance of motor symptoms (e.g., tremor, bradykinesia, rigidity) [2]. However, pathological changes in PD, including Lewy body depositions in the anterior olfactory nucleus and the brainstem of patients, occur long before motor symptoms are noticeable [3]. Such early preclinical stages of disease progression could potentially provide useful markers to identify individuals at risk of developing PD before classical clinical manifestations of the disease.

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1. REM sleep behaviour disorder and olfactory impairments: risk factors for PD

One of the strongest predictors of PD is a diagnosis of REM sleep behaviour disorder (RBD), since up to 65 % of patients that have been diagnosed with RBD will develop PD over a 10-year period [4]. RBD is a parasomnia that is characterized by the loss of muscle atonia during REM-sleep which leads to motor activity during dreaming [5]. Furthermore, compared to the general RBD population, those who also demonstrate olfactory deficits have been shown to have an elevated probabilty of developing neurodegenerative diseases such as PD within three to five years [6], suggesting that hyposmia is an additional marker for the development of PD in RBD patients. Hyposmia has also been identified as one of the earliest symptoms of PD, and it is present in about 96 % of PD patients [7]. A diagnosis of RBD and the presence of hyposmia, however, are not specific for the development of PD because they are also associated with the development of other movement disorders [8] or clinical conditions, for example, dementia [9]. A potential source of other features that could help to identify the risk of developing PD is diffusion tensor imaging (DTI), which is one modality that has been proposed to identify brain changes in PD patients [10] and might therefore be useful in combination with olfactory function tests to identify those RBD patients at highest risk of conversion to PD.

1.1. Using diffusion tensor imaging to detect prodromal signs of PD

DTI indicates the principal direction of water molecule diffusion in brain tissues and provides information about the integrity of structural connections (i.e., white matter tracts) within the brain [11]. Measures derived from DTI data include fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). These metrics are typically used to investigate potential aberrant white matter structure and integrity [11,12].

DTI has revealed aberrant white matter in the corticospinal tract (CST) in patients with PD compared with healthy individuals [13], suggesting that CST abnormalities of this nature could be potential biomarkers of PD. Mole et al. [14] reported elevated FA (bilaterally) and right AD in the CST in PD patients compared to healthy individuals. They suggested that these abnormalities may either represent compensatory changes in the form of higher axonal density and axonal sprouting, or selective neurodegeneration leading to reduced branching of neurons and reduced axonal diameter, which further restricts diffusion along the primary direction of the tract [14]. Abnormalities of white matter structure of the CST in the form of elevated FA have been consistently shown in PD patients across studies as reported in a *meta*-analysis [15]. However, much heterogeneity for FA values across studies exists and more research is needed to determine whether DTI of the CST is a reliable marker of PD.

Few studies have assessed CST integrity in RBD patients or compared DTI findings in RBD and PD patients. One of the few studies has, however, compared idiopathic RBD patients and PD patients and has shown that idiopathic RBD patients have higher MD in the right CST relative to PD patients [16]. In this study, the PD group had few symptoms of RBD. Therefore, more severe neurodegeneration accompanied by disrupted white matter integrity may only occur in PD patients with RBD [16]. Unlike other studies, however, this study did not observe differences in DTI features between patient groups and healthy controls, perhaps because of methodological differences in DTI data analyses.

DTI examination of the CST may prove useful in detecting at an early stage the onset of PD in RBD patients; however, this possibility remains uncertain because there are inconsistent results and few studies that assessed both patient groups. In addition, there is a lack of studies that investigated the CST in only hyposmic RBD patients who are at increased risk of developing PD, compared to PD patients and controls. The goal of this study was to investigate whether abnormalities in brain white matter can be seen in the CST of PD patients and whether aberrant CST integrity could potentially serve as an early marker for the presence of early PD in hyposmic RBD patients. Based on previous research [15], we hypothesized that PD patients would have elevated FA values, as well as abnormal MD, AD, and RD values compared to healthy controls. We further hypothesized that if CST abnormalities are predictors of the development of PD, we would expect that hyposmic RBD patients have abnormal CST characteristics compared to controls as well.

2. Methods

2.1. Participants

Patients with early-stage PD ($n = 32$) were between Hoehn and Yahr stages 1–2.5 [17] and were diagnosed by a qualified neurologist (RM, KS), who also administered the Unified Parkinson Disease Rating Scale Part III (UPDRS-III). Patients with idiopathic RBD ($n = 21$) were diagnosed by a qualified sleep specialist (GP) which was polysomnographically verified. RBD patients were included if they scored within the hyposmic range of the University of Pennsylvania Smell Identification Test (UPSIT; see below), based on age and gender norms. Age- and gender-matched healthy control subjects (HCs, $n = 32$) were eligible to participate if they scored over 30 out of 40 on the UPSIT and if they did not have a first-degree relative that had been diagnosed with PD. Further inclusion criteria for all participants were being between 45 and 75 years old, having no contraindications to MRI scanning, and having no other neurological or psychiatric disorders that required ongoing treatment, except for PD or RBD.

PD patients were recruited from the Movement Disorder Clinic, Division of Neurology, at Nova Scotia Health, Halifax, Canada. Five PD patients included in this study also had a confirmed diagnosis of RBD as they converted from RBD to PD prior to this study. RBD patients were recruited from the QEII Health Sciences Centre Sleep Disorders Clinic as well as a private practice in sleep medicine. HCs were recruited through online advertising and advertisement board notices. The proposed study was approved by the Nova Scotia Health Authority Research Ethics Board (IRB#2007-224) and participants had to provide informed consent to participate in the study.

2.2. Olfactory testing: the University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT is a widely used test of odour identification [18]. The test includes four booklets of 10 pages each. A patch which encapsulates a specific odour is present on each separate page and participants are required to release the odour by scratching the patch. After smelling the odour, participants must choose which option out of four provided answers best describes the odour, and participants are encouraged to guess even when no odour was perceived. The outcome measure of this test is the total number correct out of 40.

2.3. Procedure

After verifying that all inclusion criteria were met, eligible participants signed the required consent materials, filled out a demographic questionnaire, performed the UPSIT, and completed an MRI safety screening questionnaire. During the MRI scan, participants were instructed to remain still to reduce noise and artifacts. Their arms were placed on pads to further reduce motion. The MRI session took approximately 45 min to complete; structural, resting-state functional MRI, and DTI measures were taken. The current report is focused on the analysis of DTI measures. Monetary compensation was provided to all participants for taking part in the study.

2.4. Imaging acquisition, preprocessing, and DTI analysis

As part of a larger study, MRI data were collected on a 1.5 T GE Signa

HDx scanner using an 8-channel HD head coil. During each scan session, a high-resolution anatomical and a diffusion-weighted sequence were collected. Details of the MRI acquisition parameters and sequences used for this study can be reviewed in the Supplementary material.

Diffusion-weighted imaging data were preprocessed and analysed with FMRIB Software Library (FSL) version 6.0.1. Anatomical T1w and diffusion-weighted imaging (DWI) data preprocessing for each participant included brain-extraction (BET), and registration to the MNI152 template using 12-DOF linear registration (FLIRT), followed by non-linear registration (FNIRT). DWI data preprocessing also included eddy current distortions and motion artifact corrections (EDDY), and rotating b-vectors to account for head movements. DWI data were co-registered to each participant's T1w image using rigid-body 6-DOF (FLIRT) in order to map DTI values to structural images, and then the transformation matrix determined from normalizing the T1w image to the MNI152 template was applied to the outputs of diffusion tensor calculations (see below) to bring the results into standard space. Prior to tractography, we visually reviewed the quality of each participant's preprocessed DWI, brain segmentations, and non-linear registrations to the MNI 152 template space.

From the preprocessed DWI data, the diffusion tensor was calculated for each brain voxel using DTIFIT, creating output maps for eigenvalues (L1, L2, L3), eigenvectors (V1, V2, V3), FA, and MD. Probabilistic tractography was used to track and visualize white matter fibers by estimating the highest likelihood of bilateral CST orientation at every voxel and by creating a probability map of CST connectivity from one voxel to the next by repeated streamlining [19]. To conduct probabilistic tractography, BEDPOSTX was used to model crossing fibers (two per voxel) for each brain voxel using single-shell model and 5000 iterations. PROBTRACKX was used to produce streamlined fibers of each left and right CST from left and right seed mask ROI of the bilateral primary motor cortex (BA4p) into termination mask ROIs of the bilateral mediolateral cerebral peduncles (see the Supplementary material for details). An angle threshold of 45° was used to ensure correct tractography of the CST [11]. Fiber tracking stopped with a FA threshold of lower than 0.2 to preclude the inclusion of voxels with high tissue content other than white matter, and to avoid multiple fiber orientations.

Subject left and right CST probabilistic results output from PROBTRACKX were thresholded at 100 and binarized to create the final CST masks and the means of underlying voxel values for FA, AD, RD, and MD were obtained. Each participant's CST was visually inspected in both T1w-space and MNI152-space to ensure the quality and accuracy of CST tractography. The left and right tractography-based CSTs in a single subject are depicted in Fig. 1. Fig. 2 shows the probabilistic maps of the left and right CSTs compared across participant groups. The visual comparison of group-averaged tracts demonstrates a large overlap between groups which indicates that the consistency of tractography was adequate. The researcher conducting the preprocessing and first-level analyses (LP) was blinded to the group identity of participants.

2.5. Statistical analyses

The averages of each of the DTI-derived metrics from the left and right CST were compared between groups with one-way ANOVAs and Tukey's post hoc tests. Resulting p-values from each ANOVA were corrected for multiple comparisons with Bonferroni adjustments. A further separate ANOVA was done to assess group differences when PD participants with confirmed RBD are excluded. Furthermore, separate ANOVAs were conducted to assess differences in age and UPSIT scores between the groups. A Pearson Chi-Square test was used to assess differences in discrete variables and Pearson correlation analyses were used to assess correlations between DTI-derived metrics and demographic variables for each group. An independent samples *t*-test was

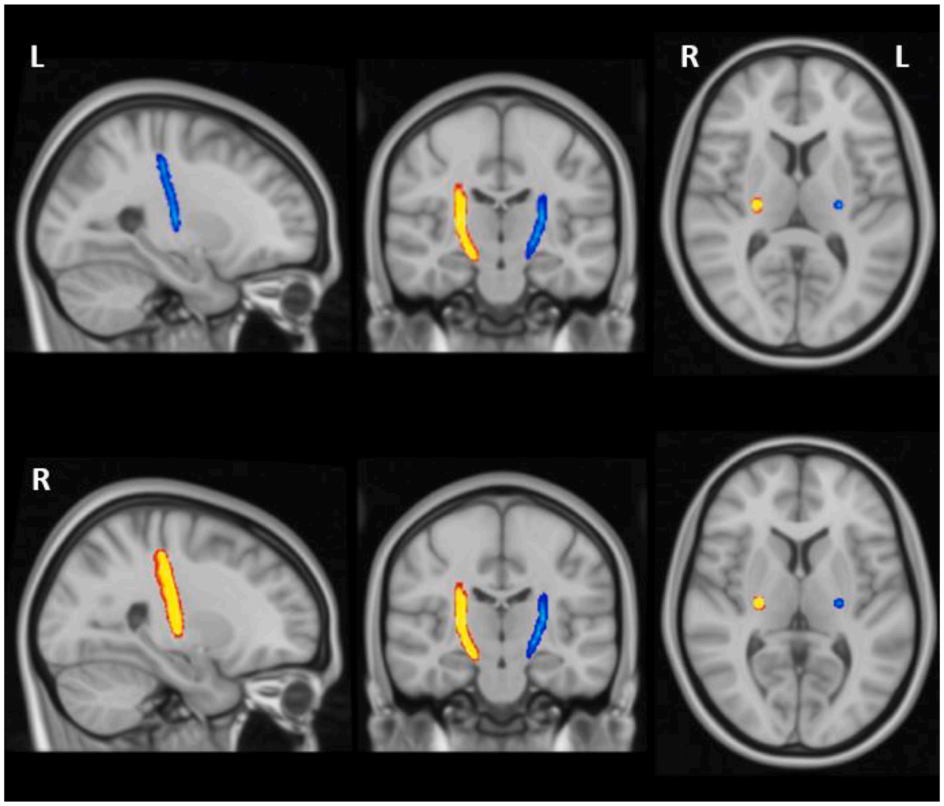

Fig. 1. Single-Subject Left and Right Corticospinal Tract Visualized with Probabilistic Tractography. *Note*. Single-subject left (blue) and right (red) corticospinal tracts overlaid on the standard MNI152_T1_1mm brain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

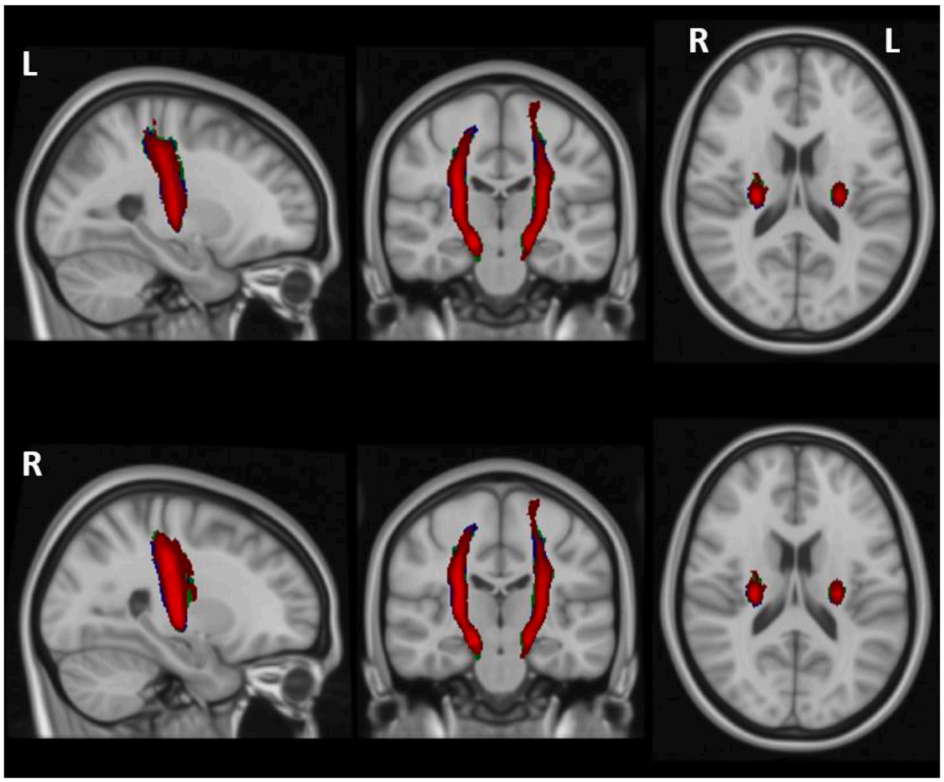

Fig. 2. Group Comparison of Probabilistic Maps of the Right and Left Corticospinal Tracts. *Note.* Group comparison of probability maps of the left and right corticospinal tracts overlaid on the standard MNI152_T1_1mm brain. Red = RBD group, green = PD group, blue = HC group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

applied to assess differences between PD patients with and without confirmed RBD. Statistical analyses were performed in SPSS (Version 25). The significance level was set to $p < .05$.

3. Results

3.1. Demographic and olfactory test data

Participant groups did not differ significantly in age nor were there significant sex differences across groups. However, there were significant differences in UPSIT scores ($\eta_p^2 = 0.638$). HCs had significantly higher UPSIT scores compared to the PD group ($p < .001$, Hedges' g = 2.887) as well as the RBD group ($p < .001$, Hedges' g = 3.369). The RBD group did not differ significantly from the PD group in olfactory function ($p > .05$). Mean scores for each group are shown in Table 1.

Five patients were concurrently diagnosed with PD and RBD. PD patients with RBD demonstrated significantly lower UPSIT scores (M = 14.6, SD = 2.79) compared to PD patients without confirmed RBD (M = 22.38, SD = 7.12; $p = .024$. Hedges' g = 1.16). There were no differences in age, disease duration, UPDRS-III scores, or Hoehn and Yahr scores between the PD subgroups.

Table 1
Demographic Information for Participant Groups.

	PD	RBD	HC	*F* (2,71)	*p*
N	31	20	29	–	–
Sex (male/female)	19/12	16/4	15/14	–	0.131*
Age (years)	62.90 (6.01)	61.65 (6.56)	60.45 (5.72)	0.437	0.297
UPSIT score	21.13 (7.20)	19.75 (7.45)	36.72 (2.22)	33.006	**<0.001**
Disease duration (years since diagnosis)	3.19 (3.26)	0.70 (0.68)	–	–	–
Hoehn & Yahr stage	1.77 (0.59)	–	–	–	–
UPDRS-III score	23.38 (11.16) †	–	–	–	–

Note. Means (standard deviations) are shown for continuous variables. Bold value indicates a significant observation ($p < .05$). * p-value from chi-squared test, $\chi 2(2) = 5.38$. † n = 24.

3.2. DTI metrics

After tractography of the CST was performed in all participants, one PD participant, one RBD participant, and three HC participants were excluded from the analysis as their tracts could not be reconstructed, possibly due to poor data quality. Thus, 31 PD patients, 20 RBD patients, and 29 healthy controls (see Table 1 for demographic information) were included in the final analyses.

For the left CST, there were no significant differences between PD, RBD, and HC groups in FA, MD, AD, or RD after correcting for multiple comparisons. Furthermore, in the right CST, there were no significant differences between groups in FA, AD, or RD. However, groups differed significantly on mean MD values in the right CST ($\eta_p^2 = 0.129$) after multiple comparison correction. RBD patients had significantly higher MD values than HCs ($p = .005$, Hedges' g = 0.856). There was a trend of higher MD values in right CST MD values in the PD group compared to HCs ($p = .051$, Hedges' g = 0.667). RBD and PD patients did not differ from each other ($p = .508$). Mean values of DTI metrics for each group are shown in Table 2.

Independent samples t-tests between PD patients with and without RBD resulted in no significant differences in any DTI metrics between the two groups. Moreover, the reported right CST mean MD group differences between RBD and HC participants were retained when excluding the five PD patients with confirmed RBD from the analysis ($p = .005$, Hedges' g = 0.856); however, the trend of higher mean MD

Table 2
Corticospinal Tract (CST) Statistics.

	PD	RBD	HC	*F* (2,77)	*p (uncorrected)*	*p (corrected)*
Mean FA (*SD*)						
left CST	0.554 (0.0274)	0.550 (0.0299)	0.561 (0.0292)	0.957	0.388	1.000
right CST	0.535 (0.0267)	0.537 (0.0306)	0.541 (0.0236)	0.388	0.680	1.000
Mean MD (*SD*)						
left CST	0.000787 (0.000024)	0.000786 (0.000029)	0.000770 (0.000029)	3.461	0.036	0.288
right CST	0.000807 (0.000021)	0.000814 (0.000028)	0.000792 (0.000024)	5.704	0.005	**0.040**
Mean AD (*SD*)						
left CST	0.00134 (0.000052)	0.00133 (0.000073)	0.00132 (0.000051)	0.859	0.428	1.000
right CST	0.00135 (0.00005)	0.00136 (0.000069)	0.00133 (0.000048)	2.624	0.079	0.632
Mean RD (*SD*)						
left CST	0.00051 (0.000027)	0.000512 (0.000024)	0.000494 (0.000032)	3.037	0.054	0.432
right CST	0.000536 (0.000025)	0.00054 (0.000025)	0.000524 (0.000026)	3.068	0.052	1.000

Note. Bold value indicates a significant observation after Bonferroni multiple comparison correction ($p < .05$).

values in the PD group compared to the HC group was absent ($p = .094$). No other significant differences were found when excluding PD patients with confirmed RBD.

3.3. Correlations with demographic variables

There was a significant correlation between UPDRS-III scores and mean MD values of the right CST within the PD group ($r = 0.493$, $p = .014$). Additionally, there was a significant correlation between UPSIT scores and mean MD ($r = -0.408$) as well as mean RD ($r = -0.531$) in the right CST within the HC group. A higher age was also related to higher mean RD of the right CST ($r = 0.428$) in the HC group. No significant correlations were found in the RBD group.

4. Discussion

This study employed DTI to investigate whether PD patients exhibit abnormal structural characteristics of the CST compared with healthy individuals. It also examined whether idiopathic RBD patients with hyposmia exhibit CST abnormalities similar to those of PD patients in order to investigate whether this could constitute an additional prodromata of PD. Contrary to our hypothesis, PD patients did not exhibit higher FA values or changes in MD, AD, and RD values compared to HCs, suggesting that CST alterations are not markers of early-stage PD. However, there was a trend of increased MD values in the PD group compared to HCs (which was not sustained when patients with concurrent PD and RBD were removed from the analysis). Our main finding was that MD of the right CST was significantly higher in hyposmic RBD patients compared to HCs. Thus, we propose that hyposmic RBD patients have abnormal white matter integrity of the CST, but that abnormal CST characteristics in this at-risk group do not seem to be clear markers of preclinical PD without comorbid RBD.

MD describes the average water diffusivity within a voxel and can reveal alterations in the extracellular space of white matter and in potential barriers to diffusion [11]. Our finding that CST abnormalities may not be a specific marker of early-stage PD is inconsistent with the outcomes of a previous *meta*-analysis that concluded that PD patients show changes of the CST structure (i.e., increased FA) [15]. Differences in defining the CST during tractography may have led to different results. Tractography conducted for our study terminated in the midbrain (mediolateral cerebral peduncles) whereas previous studies which reported CST abnormalities in PD patients included pontine CST fibers as well [14]. Lower brain regions such as the medulla oblongata and the pontine tegmentum also show pathological changes in early preclinical stages of PD [3]. Thus, excluding lower brainstem fibers may have contributed to our finding that early PD patients did not significantly differ from HCs in CST DTI metrics because abnormalities may be present mainly in those sections of the CST. Our results are similar to Lu et al. [20], who also reported that PD patients did not differ from controls on DTI metrics for the CST after conducting tractography. However, contrary to Lu et al. [20], we saw a trend of increased MD values of the right CST in PD patients compared to controls, suggesting that some PD patients may show CST alterations. It may not be surprising that study results vary because a *meta*-analysis of this issue reported high levels of heterogeneity among studies [15].

Our finding of elevated MD in the right CST of RBD patients has also been reported by Ohlhauser et al. [16]. However, that study reported MD differences in the right CST between RBD patients and PD patients, indicating that RBD patients have more severe degeneration of the CST than PD patients. These results may be accounted for by the hypothesis that white matter anomalies in the right CST are specific to RBD patients, so the observed differences were the result of a majority of PD patients not having a confirmed diagnosis of RBD in that study [16]. In contrast to Ohlhauser et al., we report here differences in DTI findings between hyposmic RBD patients and healthy control participants, and no significant differences between patient groups. The differences in study outcomes could be due to methodological differences. Ohlhauser and colleagues [16] used a whole-brain approach (tract-based spatial statistics) which is more exploratory in nature compared to tractography because the whole brain approach does not focus on specific brain regions that are hypothesized to show aberrant white matter structure [21]. As a more directed approach in finding potential differences, examining a specific region of interest also decreases the multiple comparison problem by requiring fewer statistical comparisons since fewer voxels are being examined [22]. Thus, the probability of having false positive results (i.e., obtaining a significant result that is due to chance) is reduced. Moreover, it is unclear how many RBD patients in Ohlhauser et al. [16] had hyposmia and whether including only RBD patients with hyposmia in our study may have led to different results. The presence of hyposmia in RBD patients is considered a further risk factor for PD development [6] and hyposmia is typically present before PD is clinically diagnosed [23]. Therefore, our patient groups may not differ in CST characteristics due to the higher risk of hyposmic RBD patients to develop PD. We also report that increased MD of the CST is related to higher UPDRS-III scores, and thus, more severe motor impairment in the PD group. This association indicates that the presence

of CST abnormalities in individuals at higher risk of PD may also be associated with the development of PD-related motor symptoms.

Consistent with Ohlhauser et al. [16], the majority of PD patients included in our study did not have a confirmed diagnosis of RBD, which supports the notion that MD abnormalities of the right CST are related to a RBD diagnosis. However, we included five PD patients who converted from RBD to PD and it is possible that further patients had undiagnosed symptoms of RBD as well (a measure of RBD symptoms was not included in this study). The inclusion of PD patients with comorbid RBD could have led to the finding that PD patients tended to show increased MD values similar to our RBD patients, suggesting that the presence of RBD in PD is related to CST abnormalities. Thus, abnormal CST characteristics in individuals at higher risk of PD may be an early marker of PD with comorbid RBD. Our finding that the trend was absent when PD patients with RBD were excluded from the analysis supports this idea. Yet, this also implies that PD patients with RBD would differ in CST characteristics from PD patients without RBD. We did not find such differences, however. These null findings could have been influenced by the low sample size of the PD with RBD group and the possibility of the presence of RBD symptoms in PD patients without confirmed RBD. Further studies including a group of PD patients with, and a group of PD patients without a concurrent diagnosis of RBD would help to clarify this issue. Recently, Ansari et al. [24] demonstrated that PD patients with concurrent RBD demonstrated significant white matter integrity differences in the bilateral CSTs compared to PD patients without RBD. This finding implies that compared to PD patients without RBD, the presence of RBD in PD is related to worse white matter degeneration in this region and could also be associated with earlier progression of motor symptoms [24]. Consequently, it is possible that the white matter abnormality in our sample of RBD patients is a marker of the progression towards PD-related motor signs in early PD patients who also have RBD, but not in those without diagnosed RBD. Our PD patients with diagnosed RBD also showed lower olfactory functioning scores compared to PD patients without confirmed RBD. Impaired olfactory functioning has been related to an increase in motor and non-motor symptoms in PD, and it was suggested that olfactory function may be a marker of disease progression [25]. Therefore, reduced olfactory functioning in PD patients with RBD may indicate that PD patients with RBD may experience a more severe course of the disease compared to PD patients without RBD.

As the main motor pathway transferring information from the brain to the spinal cord, the CST is involved in controlling voluntary movement [26] and abnormalities in this structure may therefore have implications for motor symptomatology. The finding of changes only in the right CST suggests that potential early markers of disease progression are lateralized to one hemisphere [16]. This lateralization of CST alterations is consistent with a study reporting that a majority of PD patients showed unilateral motor symptoms and structural changes in the contralateral hemisphere, especially in early stages of PD [27]. Hence, RBD patients who will develop PD in the future may eventually show early motor signs on the left side of the body because changes in white matter structure were found in the right hemisphere which may lead to motor symptoms in the contralateral side of the body. Nevertheless, more research is needed to investigate the unilaterality of CST abnormalities as found in this study, as previous reports demonstrated bilateral CST changes [14,15]. Kim et al. [28] found that right-handed early PD patients who have left-sided motor symptoms showed less cortical thinning in the left hemisphere. They concluded that this could be due to neuroprotective effects on the contralateral motor cortex of their dominant hand side, caused by the dominant hand's increased motor activity. As the majority of participants in our study were right-handed, it could be possible that hyposmic RBD patients who may be developing PD do not show abnormalities in the left CST due to neuroprotective mechanisms affecting motor pathways within the left hemisphere.

5. Limitations and future directions

One limitation of this study is that we could not assess longitudinal outcomes so that we do not know whether the hyposmic RBD patients included in our study will eventually develop PD, and whether the combination of CST white matter alterations and hyposmia would constitute a prodromal sign of PD in the RBD patients. It is possible that some hyposmic RBD patients of this study who also exhibited CST abnormalities may develop a neurodegenerative disease other than PD because hyposmia and RBD have also been related to dementia with Lewy bodies and multiple system atrophy (MSA) [8,9] and research has shown that abnormalities in DTI metrics of the CST, namely elevated MD, have also been reported in MSA [29]. Future longitudinal studies should investigate the incidence of RBD patients who have CST abnormalities and hyposmia of developing PD or other neurodegenerative illnesses.

Probabilistic tractography also has limitations. For example, tractography indirectly assesses white matter tracts and only infers their location based on the direction of water molecule diffusion. The anatomical accuracy seems to be relatively poor because tracts assessed with tractography methods do not seem to match known tracts that were mapped with injections of axonal tracers in animal models [30]. Precise tracking and the reconstruction of a given tract can also be influenced by systematic errors within data acquisition and analysis pipelines [31]. As well, differences in MRI scanners, scanning parameters, and analysis tools can be expected to contribute to variability between studies. For instance, most current studies use 3 T MRI scanners which offer a higher sensitivity compared to 1.5 T scanners. Therefore, future studies examining the CST in individuals at risk of PD may be able to detect further abnormalities in DTI metrics which were not detected in the present study. DTI tractography is nonetheless a useful and promising non-invasive method that can offer important insights into disease-related changes in the white matter of the brain [30]. One further limitation of this study is that we did not assess other brain tracts in addition to the CST. Comparing other tracts' DTI results with our findings could give us more insight into the specificity of the reported group differences and into the role of the CST in RBD pathology.

It would be advantageous for future research to analyse different sections of the bilateral CST (e.g., lower, middle, and upper CST) which could help to determine whether abnormalities are localized along the CST or involve the whole tract. The neuropathology of RBD has been characterized by anatomical and functional abnormalities in brainstem regions of the pons [32], suggesting that brainstem regions are more likely to show alterations compared to higher brain regions. Pathological changes related to PD begin in lower brain regions such as the brainstem as well [3]. Thus, it is possible that both RBD and early PD patients exhibit early white matter alterations in lower CST areas which may be indicative of disease progression. Moreover, it would be interesting for future research to evaluate potential differences in the structural characteristics of the CST between idiopathic RBD patients with hyposmia and PD patients with comorbid RBD in order to determine whether the presence of CST abnormalities is a biomarker of this subtype of PD patients.

6. Conclusion

This study demonstrated that hyposmic RBD patients exhibit changes in white matter integrity of the right CST, namely increased mean diffusivity, compared to healthy individuals. Most PD patients appear not to have such abnormalities in the CST, indicating that the identified abnormal DTI metrics of the CST are not biomarkers for early PD in the absence of RBD. However, we suggest that CST abnormalities may be related to the development of PD with comorbid RBD. Longitudinal research is needed to assess whether the presence of RBD, hyposmia, and white matter abnormalities increases the risk of developing a neurodegenerative disease in the future.

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CRediT authorship contribution statement

Laura J. Pimer: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Ronald A. Leslie:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Gosia Phillips:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Aaron J. Newman:** Methodology, Writing – review & editing, Formal analysis. **Benjamin Rusak:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Tyler M. Rolheiser:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Kerrie Schoffer:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **M. Naeem Khan:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **J. Roger McKelvey:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Harold A. Robertson:** Conceptualization, Methodology, Validation, Investigation, Writing – review & editing, Funding acquisition. **Kimberley P. Good:** Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] L. de Lau, M. Breteler, Epidemiology of Parkinson's disease, Lancet Neurol. 5 (2006) 525–535, https://doi.org/10.1016/S1474-4422(06)70471-9.
[2] J. Jankovic, Parkinson's disease: Clinical features and diagnosis, J. Neurol. Neurosur. Ps. 79 (2008) 368–376, https://doi.org/10.1136/jnnp.2007.131045.
[3] H. Braak, K. Del Tredici, U. Rüb, R. de Vos, E.N. Jansen Steur, E. Braak, Staging of brain pathology related to sporadic Parkinson's disease, Neurobiol. Aging 24 (2003) 197–211, https://doi.org/10.1016/S0197-4580(02)00065-9.
[4] R.B. Postuma, D. Aarsland, P. Barone, D.J. Burn, C.H. Hawkes, W. Oertel, T. Ziemssen, Identifying prodromal Parkinson's disease: Pre-motor disorders in Parkinson's disease, Movement Disord. 27 (2012) 617–626. https://doi-org.10.1002/mds.24996.
[5] W.H. Oertel, C. Depbovlu, M. Krenzer, D. Vadasz, V. Ries, F. Sixel-Döring, G. Mayer, REM sleep behaviour disorder as a prodromal stage of α-synucleinopathies: Symptoms, epidemiology, pathophysiology, diagnosis and therapy, Nervenarzt 85 (2014) 19–25, https://doi.org/10.1007/s00115-013-3891-8.
[6] R.B. Postuma, J.F. Gagnon, J.A. Bertrand, D. Génier, J.Y. Montplaisir, Parkinson risk in idiopathic REM sleep behaviour disorder: Preparing for neuroprotective trials, J. Neurol. 84 (2015) 1104–1113, https://doi.org/10.1212/WNL.0000000000001364.
[7] A. Haehner, S. Boesveldt, H.W. Berendse, A. Mackay-Sim, J. Fleischmann, P. A. Silburn, A.N. Johnston, G.D. Mellick, B. Herting, H. Reichmann, T. Hummel, Prevalence of smell loss in Parkinson's disease - A multicenter study, Parkinsonism Relat. D 15 (2009) 490–494, https://doi.org/10.1016/j.parkreldis.2008.12.005.
[8] C.H. Schenck, B.F. Boeve, M.W. Mahowald, Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: A 16-year update on a previously reported series, Sleep Med. 14 (2013) 744–748, https://doi.org/10.1016/j.sleep.2012.10.009.
[9] R.H. McShane, Z. Nagy, M.M. Esiri, E. King, C. Joachim, C. Sullivan, A.D. Smith, Anosmia in dementia is associated with lewy bodies rather than Alzheimer's pathology, J. Neurol. Neurosur. Ps. 70 (2001) 739, https://doi.org/10.1136/jnnp.70.6.739.
[10] T.M. Rolheiser, H.G. Fulton, K.P. Good, J.D. Fisk, J.R. McKelvey, C. Scherfler, N. M. Khan, R.A. Leslie, H.A. Robertson, Diffusion tensor imaging and olfactory identification testing in early-stage Parkinson's disease, J. Neurol. 258 (2011) 1254–1260, https://doi.org/10.1007/s00415-011-5915-2.
[11] D. Le Bihan, Looking into the functional architecture of the brain with diffusion MRI, Nat. Revs. Neurosci. 4 (2003) 469–480, https://doi.org/10.1038/nrn1119.
[12] M.D. Budde, J.H. Kim, H. Liang, R.E. Schmidt, J.H. Russell, A.H. Cross, S. Song, Toward accurate diagnosis of white matter pathology using diffusion tensor imaging, Magn. Reson. Med. 57 (2007) 688–695, https://doi.org/10.1002/mrm.21200.
[13] K.I. Taylor, F. Sambataro, F. Boess, A. Bertolino, J. Dukart, Progressive decline in gray and white matter integrity in de novo Parkinson's disease: An analysis of longitudinal Parkinson progression markers initiative diffusion tensor imaging data, Front. Aging Neurosci. 10 (2018) 318, https://doi.org/10.3389/fnagi.2018.00318.
[14] J.P. Mole, L. Subramanian, T. Bracht, H. Morris, C. Metzler-Baddeley, D.E. Linden, Increased fractional anisotropy in the motor tracts of Parkinson's disease suggests compensatory neuroplasticity or selective neurodegeneration, Eur. Radiol. 26 (2016) 3327–3335, https://doi.org/10.1007/s00330-015-4178-1.
[15] C. Atkinson-Clement, S. Pinto, A. Eusebio, O. Coulon, Diffusion tensor imaging in Parkinson's disease: Review and meta-analysis, NeuroImage-Clin. 16 (2017) 98–110, https://doi.org/10.1016/j.nicl.2017.07.011.
[16] L. Ohlhauser, C.M. Smart, J.R. Gawryluk, Tract-based spatial statistics reveal lower white matter integrity specific to idiopathic rapid eye movement sleep behaviour disorder as a proxy for prodromal Parkinson's disease, J. Parkinson Dis. 9 (2019) 723–731, https://doi.org/10.3233/JPD-191688.
[17] M.M. Hoehn, M.D. Yahr, Parkinsonism: Onset, progression, and mortality, Neurology 17 (1967) 427–442, https://doi.org/10.1212/wnl.17.5.427.
[18] R.L. Doy, M.G. Newhouse, J.D. Azzalina, Internal consistency and short-term test-retest reliability of the University of Pennsylvania Smell Identification Test, Chem. Sens. 10 (3) (1985) 297–300.
[19] G.J. Parker, H.A. Haroon, C.A. Wheeler-Kingshott, A framework for a streamline-based probabilistic index of connectivity (PICo) using a structural interpretation of MRI diffusion measurements, J. Magn. Reson. Imaging 18 (2003) 242–254, https://doi.org/10.1002/jmri.10350.
[20] M. Lu, C. Chun-Ming, D. Jeng-Ren, U. Ziemann, C. Jui-Cheng, C. Shang-Ming, T. Chon-Haw, Investigation of motor cortical plasticity and corticospinal tract diffusion tensor imaging in patients with parkinsons disease and essential tremor, PLoS One 11 (2016) e0162265.
[21] M. Froeling, P. Pullens, A. Leemans, DTI analysis methods: Region of interest analysis, in: W. Van Hecke, L. Emsell, S. Sunaert (Eds.), Diffusion Tensor Imaging, Springer, New York, 2016, pp. 175–182, https://doi.org/10.1007/978-1-4939-3118-7_9.
[22] S.M. Smith, M. Jenkinson, H. Johansen-Berg, D. Rueckert, T.E. Nichols, C. E. Mackay, K.E. Watkins, O. Ciccarelli, M.Z. Cader, P.M. Matthews, T.E. Behrens, Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data, NeuroImage 31 (2006) 1487–1505, https://doi.org/10.1016/j.neuroimage.2006.02.024.
[23] M.J. Armstrong, M.S. Okun, Diagnosis and treatment of Parkinson disease, JAMA 323 (2020) 548–560, https://doi.org/10.1001/jama.2019.22360.
[24] M. Ansari, F. Rahmani, M. Dolatshahi, A. Pooyan, M.H. Aarabi, Brain pathway differences between Parkinson's disease patients with and without REM sleep behaviour disorder, Sleep Breath. 21 (2017) 155–161, https://doi.org/10.1007/s11325-016-1435-8.
[25] D.S. Roos, J.W. Twisk, P.G. Raljmakers, R.L. Doty, H.W. Berendse, Hyposmia as a marker of (non-)motor disease severity in Parkinson's disease, J. Neural Transm. 126 (2019) 1471–1478, https://doi.org/10.1007/s00702-019-02074-0.
[26] O. Phillips, F. Squitieri, C. Sanchez-Castaneda, F. Elifani, A. Griguoli, V. Maglione, C. Caltagirone, U. Sabatini, M. Di Paola, The corticospinal tract in Huntington's disease, Cereb. Cortex 25 (2015) 2670–2682, https://doi.org/10.1093/cercor/bhu065.
[27] P. Riederer, K.A. Jellinger, P. Kolber, G. Hipp, J. Sian-Hülsmann, R. Krüger, Lateralisation in Parkinson disease, Cell Tissue Res. 373 (2018) 297–312, https://doi.org/10.1007/s00441-018-2832-z.
[28] J.S. Kim, J. Yang, J. Lee, J. Youn, J. Kim, J.W. Cho, Topographic pattern of cortical thinning with consideration of motor laterality in Parkinson disease, Parkinsonism Relat. D. 20 (2014) 1186–1190, https://doi.org/10.1016/j.parkreldis.2014.08.021.
[29] A. Worker, C. Blain, J. Jarosz, K.R. Chaudhuri, G.J. Barker, S.C.R. Williams, R. G. Brown, P.N. Leigh, F. Dell'Acqua, A. Simmons, Diffusion Tensor Imaging of Parkinson's disease, multiple system atrophy and progressive supranuclear palsy: A tract-based spatial statistics study, PLoS One 9 (2014) e112638.
[30] C. Thomas, F.Q. Ye, M.O. Irfanoglu, P. Modi, K.S. Saleem, D.A. Leopold, C. Pierpaoli, Anatomical accuracy of brain connections derived from diffusion MRI

tractography is inherently limited, PNAS 111 (2014) 16574–16579, https://doi.org/10.1073/pnas.1405672111.
[31] D. Jones, Challenges and limitations of quantifying brain connectivity in vivo with diffusion MRI, J. Med. Imaging 2 (2010) 341–355, https://doi.org/10.2217/IIM.10.21.
[32] J. Suescun, T.M. Ellmore, M. Schiess, REM sleep behaviour disorder: A prodromal synucleinopathy, Curr. Geriar. Rep. 5 (2016) 95–102, https://doi.org/10.1007/s13670-016-0174-9.