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# Tractography Analysis of White Matter Pathways Associated with Speech Impairment in Parkinson's Disease

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## Abstract

**Purpose:** Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting multiple systems. Speech disorders, stemming from motor and nonmotor deficits, affect up to 89% of PD patients. This study examines the arcuate fasciculus (AF) and frontal aslant tract (FAT), white matter pathways linked to verbal fluency, which have not been previously assessed in PD.

**Methods:** We included publicly available high-quality diffusion-weighted images (DWI) acquired with 120 gradient directions (b = 2500 s/mm$^2$) from 27 PD patients (Age: 66 ± 8, 14 M, 13 F) and 26 age-, sex-, and education-matched controls (Age: 64 ± 8, 14 M, 12 F), processed using the Generalized Q-sampling Imaging (GQI) model (DSI Studio software) for white matter pathway reconstruction. The Automatic Fiber Tracking (AutoTrack) option in DSI Studio was used for virtual dissection of the AF and FAT. Diffusion metrics of mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), fractional anisotropy (FA), quantitative anisotropy (QA), and track volume measures were obtained and analyzed.

**Results:** No significant correlation was observed between quantitative anisotropy and verbal fluency measures across PD and control groups. However, male PD patients exhibited reduced left FAT volume and significantly lower QA in bilateral FAT and left AF. Microstructural changes in the FAT were observed in male PD patients, but no correlation was found between verbal fluency scores and QA.

**Conclusion:** Our results suggest a more severe impact on the microstructure of the FAT in male PD patients compared to females.

**Keywords:** diffusion MRI, parkinson's disorder, arcuate fasciculus, frontal aslant tract, speech impairment

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# Parkinson Hastalığında Konuşma Bozukluğu ile İlişkili Beyaz Cevher Yolaklarının Traktografi Analizi

**Öz**

**Amaç:** Parkinson hastalığı (PH), birden fazla sistemi etkileyen ilerleyici bir nörodejeneratif hastalıktır. Motor ve motor dışı defisitlerden kaynaklanan konuşma bozuklukları, PH hastalarının %89'unu etkiler. Bu çalışma, daha önce PH hastalarında değerlendirilmemiş, sözel akıcılıkla ilişkili beyaz cevher yolakları olan fasciculus arcuatus (AF) ve frontal aslant tractusunu (FAT) incelemektedir.

**Yöntemler:** Çalışmamıza, 27 PH (Yaş: 66 ± 8, 14 Erkek, 13 Kadın) ve 26 yaş, cinsiyet ve eğitim düzeyi eşleşmiş sağlıklı kontrole (Yaş: 64 ± 8, 14 Erkek, 12 Kadın) ait, açık erişimli difüzyon-ağırlıklı görüntü (DAG) (120 gradyan yönü, b = 2500 s/mm$^2$) dahil edilmiştir. Beyaz cevher yolaklarının yapılandırılması Generalized Q-sampling Görüntüleme (GQI) modeli kullanılarak elde edilmiştir. AF ve FAT'ın sanal diseksiyonu için DSI Studio otomatik lif takibi (AutoTrack) seçeneği kullanılmıştır. Fraksiyonel anizotropi (FA), ortalama difüzyon (MD), aksiyal difüzyon (AD), radyal difüzyon (RD), kantitatif anizotropi (QA) ve traktus hacmi gibi difüzyon ölçümleri elde edilip analiz edilmiştir.

**Bulgular:** PH ve kontroller arasında kantitatif anizotropi ile sözel akıcılık ölçümleri arasında anlamlı bir korelasyon gözlemlenmemiştir. Bununla birlikte, erkek PH grubunda sol FAT hacminde azalma ve bilateral FAT ile sol AF'de anlamlı şekilde daha düşük QA değerleri tespit edilmiştir. FAT'taki mikro yapısal değişiklikler erkek PH grubunda gözlemlenmiş, ancak sözel akıcılık puanları ile QA arasında bir korelasyon bulunmamıştır.

**Sonuç:** Bulgularımız, erkek PH hastalarında FAT mikro yapısal yapısının kadınlara kıyasla daha şiddetli etkilendiğini göstermektedir.

**Anahtar kelimeler:** difüzyon MRG, Parkinson hastalığı, fasciculus arcuatus, frontal aslant tractusu, konuşma bozukluğu.

## INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative condition following Alzheimer's disease. Motor symptoms such bradykinesia, muscular stiffness, resting tremors, and postural instability are usually the first to appear. Aside from these, a variety of non-motor symptoms such as sadness, sleep difficulties, cognitive impairment, and a decreased sense of smell may accompany the PD[1]. In addition, a combination of motor and non-motor abnormalities leads to speech impairment, affecting approximately 89% of patients[2].

The Lewy bodies (LBs) formation and progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) are key features of Parkinson's disease (PD)[3]. Changes in white matter (WM) are receiving more attention, despite the fact that it has historically been regarded as a grey matter (GM) disorder[4]. The degeneration of dopaminergic neurons and Lewy bodies accumulation are often associated with neuroglial cell damage and axonal demyelination, alongside an increase in microglia concentration in extracellular spaces[1]. These pathological changes are thought to contribute to disruptions in the structural connectivity of white matter tracts, which can be assessed using advanced imaging techniques. Diffusion magnetic resonance imaging (dMRI) is an effective tool for evaluating white matter (WM) microstructural integrity and identifying alterations linked to different neurological disorders. In addition to its role in identification of white matter integrity, dMRI facilitates tractography, enabling the mapping of specific neural pathways.

The arcuate fasciculus (AF) and frontal aslant tract (FAT) are particularly significant among white matter tracts related to language because

of their critical functions in verbal fluency[5]. AF is a long-recognized language pathway traditionally associated with supporting the repetition of verbal information. It is now suggested to play a broader role in the sensory-motor mapping of sound to articulation[6], forming both direct and indirect connections between critical language areas. Its long fibers link speech production areas (Broca's area in the left inferior frontal gyrus) with speech perception areas (Wernicke's area in the left superior temporal gyrus)[7]. In addition, AF includes shorter pathways: an anterior segment connecting Broca's area to Geschwind territory in the inferior parietal lobe (IPL) and a posterior segment linking Geschwind territory to Wernicke's area[8]. FAT is a relatively newly described tract connecting supplementary motor area (SMA) and pre-SMA in the medial frontal lobe to the inferior frontal gyrus (IFG), specifically Broca's area and particularly associated with a various speech and language functions such as verbal fluency, initiation and inhibition of speech, sentence production, and lexical decision[9,10]. Patients with lesions affecting the FAT exhibit deficits in fluency and may develop mutism. These findings, as suggested by studies, indicate that the FAT is involved in motor planning, particularly in functions related to vocalization and speech. These two tracts together -FAT and AF- identified to be the key bundles that may be involved in predictive coding in speech[7].

In the past decade, growing focus has been placed on the influence of biological sex in PD development, alongside factors like age, genetics, environmental exposures, and immune status[11]. Notable sex-based differences have been observed in the disease's epidemiological and clinical characteristics such as men are affected twice as often as women, yet women tend to experience higher mortality rates and faster disease progression[11]. Despite growing interest in WM changes in PD, microstructural alterations in the AF and FAT have not been thoroughly assessed. Moreover, the relationship between WM integrity, sex differences, and verbal fluency in PD remains underexplored. We hypothesized that verbal fluency and the microstructural characteristics of these white matter pathways, as well as sex, would be closely linked to damage to the AF and FAT. This study addresses these questions by utilizing Generalized Q-sampling Imaging (GQI) to map the AF and FAT, investigate the alterations of WM diffusivity in PD, and analyze the effects of sex and verbal fluency measures. Our findings aim to contribute to a more comprehensive understanding of WM involvement in PD and its clinical implications.

## METHODS

### Patients and Methods

The datasets collected by other institutions and made publicly available online for research purposes were used in this study[12]. The original data collection was conducted with the approval and oversight of the respective institutions' ethical boards, and all participant information was anonymized prior to public release. Our analysis of this open-access data was conducted in accordance with the ethical approval granted by Istanbul Medipol University (Date 20/03/2022, Number E-10840098-772.02-1911).

The Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC www.nitrc.org) is a platform offering a range of resources, including image repository[13]. The high-quality diffusion-weighted imaging (DWI) dataset for Parkinson's disease was obtained from NITRC image repository. The dataset contained DWI of 27 PD patients (Age: 64 ± 8, 14 M, 13F) and 26 age (66± 8, 14 M, 12F), sex, and education-matched control subjects[12]. The details about the MRI acquisition protocols and demographic information can be reviewed on

the official webpage of the Parkinson's Disease Datasets (https://www.nitrc.org/projects/parktdi/) as well as in the Ziegler et al.'s study[12].

## Measures

The dataset from Ziegler et al.[12] also contained psychological tests. From those we used the Symbol Digit Modalities test for verbal fluency scores of categories (semantic fluency) and letters (phonemic fluency) to correlate our diffusion parameters. These tests are widely used to evaluate language abilities, executive functions, and the integrity of frontal and temporal lobe networks.

## Tractography of patient and healthy control groups

We used high-quality DWI with 120 gradient directions and a high b-value of 2500 s/mm$^2$. The GQI model (DSI Studio) was used for the reconstruction of the white matter pathways[14]. The Automatic Fiber Tracking (AutoTrack) option in DSI Studio[15] (https://dsi-studio.labsolver.org/) was used for the virtual dissection of the AF and the FAT (Figure 1). The anatomical accuracy of the tracts was independently quality-checked by two anatomists (AO and BT), who agreed not to make any manual adjustments to the AutoTrack results. Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), quantitative anisotropy (QA), and track volume measures were obtained for further statistical analysis. The tract volumes of the AF and FAT were normalized by dividing them by the total intracranial volume (ICV). The resulting values, adjusted for ICV, were used as the normalized measures, since tract volume is likely influenced by the total ICV.

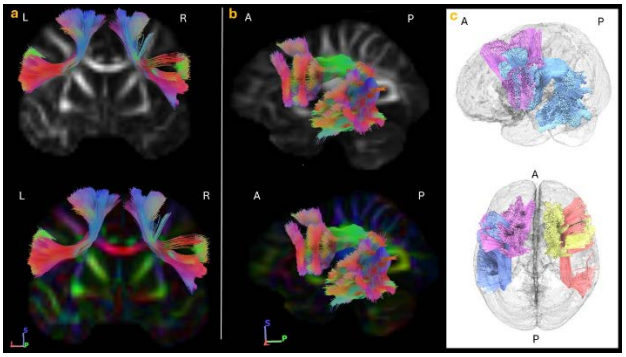


**Figure 1:** Autotract results of the FAT and AF. a) Frontal aslant tract; b) Arcuate fasciculus Upper: on QA map Lower: on color map. The fibers are in standard RGB colors. c) pseudo-colored FAT and AF on isosurface brain image Upper: left view Lower: Superior view. [A: anterior, P: posterior, L: left, R: right]

## Correlation Analysis Between Groups

To examine the relationship between verbal fluency and tract measures, correlation analyses were performed using the Pearson correlation coefficient for each group. The verbal fluency task included two subcategories: letter fluency and category fluency. The left and right AF and the left FAT, with QA measures used to assess the integrity of these tracts.

Participants were divided into male and female groups for both PD and control cohorts. The correlations between verbal fluency scores (both letter and category fluency) and the tract measurements for each group were calculated separately. The results were reviewed by an experienced neurologist (Y.E). Pearson's r values and corresponding p-values were computed to assess the strength and statistical significance of the associations. A p-value of less than 0.05 was taken as significant.

## Statistical Analysis

SPSS 30 (I.B.M., Chicago) software was used for statistical analysis and the graphs were created using the GraphPad Prism V10.4 software. The results are presented as mean values ± SD ($\bar{x}$ ± SD). The Shapiro-Wilks test was used to determine whether the parameters showed normal distribution or not. $p>0.05$ was

interpreted as showing normal distribution. T-tests were applied to the parameters that showed normal distribution, and Mann-Whitney U tests were applied to the parameters that did not show normal distribution. $p<0.05$ was interpreted as statistically significant.

## RESULTS

### Demographics of the cohort

Twenty-seven PD patients (Age: 66 ± 8, 14 M, 13F) and 26 age, sex, and education-matched controls (Age: 64 ± 8, 14 M, 12F) were included in the study. The demographics and test measures of all subjects were given in Table 1.

**Table 1:** Demographical information of the subjects (Used with permission of Elsevier, from Ziegler et al.[12] Mapping track density changes in nigrostriatal and extranigral pathways in Parkinson's disease. Neuroimage. 2014;99: 498- 508, Copyright Elsevier, 2014; permission conveyed through Copyright Clearance Center, Inc)

| | Healthy controls (*n* = 26) | Parkinson's patients (*n* = 27) | t-Test, *p*-value |
|---|---|---|---|
| Age | 64 (8) | 66 (8) | 0.549 |
| Sex (M:F) | 14:12 | 14:13 | |
| Years of education | 13 (3) | 11 (3) | 0.133 |
| ICV (mm3) | 1478 (152) | 1516 (148) | 0.36 |
| BMI (kg/m2) | 25 (3) | 25 (3) | 0.66 |
| Hand dominance (L:R) | 2:24 | 2:25 | |
| Hoehn & Yahr stage | | 1.5 (0.62) | |
| Most affected side (L:R) | | 10:17 | |
| Disease duration (years) | | 5 (3) | |
| LEDD (mg) | | 323 (255) | |
| UPDRS Section 2 | | 9 (6) | |
| UPDRS Section 3 | | 14 (7) | |
| Mattis | 139 (4) | 136 (4) | 0.004 |
| MMSE | 29 (1) | 28 (1) | 0.022 |
| HADS total | 10 (4) | 13 (6) | 0.066 |
| PDQ39 mobility | | 20 (18) | |
| PDQ39 total | | 189 (114) | |
| Rey Auditory Verbal Learning Test | 53 (11) | 44 (11) | 0.006 |
| SDMT | 51 (10) | 45 (12) | 0.062 |
| JOLO | 27 (4) | 25 (4) | 0.055 |

*Values reflect mean (st. dev.). Two-tail t-tests were performed with an assumption of unequal variance in each group. ICV = intracranial volume, BMI = body mass index, LEDD = L-DOPA equivalent daily dose[16] UPDRS = Unified Parkinson's Disease Rating Scale, MMSE = Mini Mental State Examination, HADS = Hospital Anxiety and Depression Scale, PDQ = Parkinson's Disease Questionnaire, SDMT = Symbol Digit Modalities Test, JOLO = Judgment of line orientation test.*

### Morphological features

We were able to virtually dissect the right and left AF and FAT for all subjects. The volume of these tracts was not statistically different between the groups. However, further analysis, including male-only and female-only groups with matched sex, revealed a statistically significant lower volume of left FAT in male subjects, whereas there was no difference in females. Figure 2 shows a comparative example of the virtual dissection of these tracts on PD subject and corresponding control.

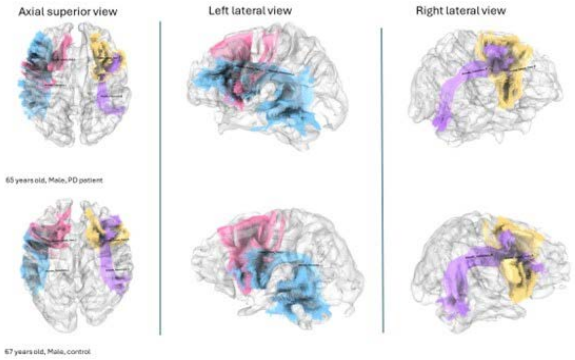


**Figure 2:** Tractography of the FAT and AF represented on an isosurface brain image. Upper row: 65 yr old Male PD patient; Lower row: 67 yr old Male control. Fibers are pseudo-colored, Fuschia (Axial and left view) and Yellow (axial and right view): FAT; Blue (Axial and left view) and Purple (Axial and Right view): AF

### Correlation with verbal fluency and QA measures

Female PD Group: No statistically significant correlation was found between verbal fluency letter scores and the QA values of the left and right FAT and AF ($p > 0.05$). Similarly, no significant correlations were observed between verbal fluency category scores and the QA values of the left and right FAT and AF ($p > 0.05$).

Female Control Group: There were no statistically significant correlations between

verbal fluency letter scores and the QA values of the left and right FAT and AF ($p > 0.05$). Additionally, no significant correlations were found between verbal fluency category scores and the QA values of the left and right FAT and AF ($p > 0.05$).

Male PD Group: No statistically significant correlation was observed between verbal fluency letter scores and the QA values of the left and right FAT and AF ($p > 0.05$). Similarly, there were no significant correlations between verbal fluency category scores and the QA values of the left and right FAT and AF ($p > 0.05$).

Male Control Group: No statistically significant correlations were found between verbal fluency letter scores and the QA values of the left and right FAT and AF ($p > 0.05$). Furthermore, there were no significant correlations between verbal fluency category scores and the QA values of the left and right FAT and AF ($p > 0.05$).

The results of the correlation analysis are given as supplementary document (Supp_table_1).

## Diffusion metrics

We quantified the FA, MD, AD, RD, QA, and track volume for left and right AF and FAT for 27 PD patients (Age: 64 ± 8, 14 M, 13F) and 26 matched controls (Age: 66 ± 8, 14 M, 12F) for the results acquired by Autotrack, DsiStudio. The diffusivity calculated in DSIStudio has a unit of 10^-3 mm^2/s. There were no statistically significant differences in the parameters between the PD group and the control group.

However, according to the uncorrected results for multiple comparisons, male individuals with PD had significantly decreased QA in the left FAT and AF, a reduced tract volume in the left FAT, and decreased QA in the right FAT compared to matched controls. On the contrary, none of the parameters showed a statistically significant difference in female individuals with PD compared to controls. Figure 3 shows the boxplots for the statistically significant parameters in males and their corresponding results in female subjects.

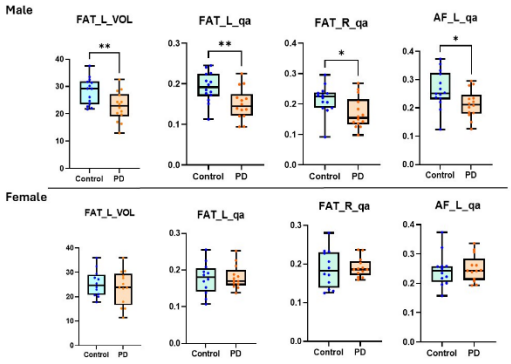


**Figure 3:** Boxplots showing the statistically significant parameters for male subjects and the corresponding results for female subjects.

**Table II:** Statistical results for the group comparisons of AF and FAT between male PD and control groups.

| Variable | PD Group (n=14) | Control Group (n=14) | P value |
|---|---|---|---|
| FAT-L | | | |
| volume | 24.74 ± 5.39 | 28.29 ± 4.89 | **0.008** |
| fa | 0.31 ± 0.03 | 0.33 ± 0.02 | 0.47 |
| md | 0.62 ± 0.03 | 0.61 ± 0.03 | 0.77 |
| qa | 0.21 ± 0.02 | 0.19 ± 0.02 | **0.008** |
| ad | 0.84 ± 0.02 | 0.83 ± 0.03 | 0.94 |
| rd | 0.52 ± 0.03 | 0.51 ± 0.03 | 0.70 |
| FAT-R | | | |
| volume | 23.19 ± 5.56 | 27.24 ± 5.39 | 0.41 |
| fa | 0.31 ± 0.03 | 0.32 ± 0.03 | 0.45 |
| md | 0.63 ± 0.03 | 0.62 ± 0.03 | 0.67 |
| qa | 0.24 ± 0.02 | 0.22 ± 0.02 | **0.025** |
| ad | 0.83 ± 0.03 | 0.83 ± 0.02 | 0.84 |
| rd | 0.48 ± 0.03 | 0.48 ± 0.03 | 0.61 |
| AF-L | | | |
| volume | 16.40 ± 5.89 | 19.00 ± 5.25 | 0.08 |
| fa | 0.35 ± 0.03 | 0.35 ± 0.03 | 0.87 |
| md | 0.62 ± 0.03 | 0.61 ± 0.03 | 0.85 |
| qa | 0.22 ± 0.02 | 0.21 ± 0.02 | **0.031** |
| ad | 0.83 ± 0.03 | 0.84 ± 0.02 | 0.75 |
| rd | 0.52 ± 0.03 | 0.52 ± 0.03 | 0.92 |
| AF-R | | | |
| volume | 20.40 ± 5.99 | 23.19 ± 5.56 | 0.26 |
| fa | 0.35 ± 0.03 | 0.36 ± 0.03 | 0.45 |
| md | 0.63 ± 0.03 | 0.62 ± 0.03 | 0.78 |
| qa | 0.24 ± 0.02 | 0.22 ± 0.02 | 0.10 |
| ad | 0.84 ± 0.03 | 0.83 ± 0.02 | 0.86 |
| rd | 0.48 ± 0.03 | 0.48 ± 0.03 | 0.78 |

**Table III:** Statistical results for the group comparisons of AF and FAT between female PD and control groups

| Variable | PD Group (n=13) | Control Group (n=12) | P value |
|---|---|---|---|
| FAT-L | | | |
| volume | 23.76 ± 6.59 | 25.39 ± 5.14 | 0.53 |
| fa | 0.31 ± 0.03 | 0.33 ± 0.02 | 0.73 |
| md | 0.62 ± 0.03 | 0.61 ± 0.03 | 0.91 |
| qa | 0.21 ± 0.02 | 0.19 ± 0.02 | 0.82 |
| ad | 0.84 ± 0.02 | 0.83 ± 0.03 | 0.83 |
| rd | 0.52 ± 0.03 | 0.51 ± 0.03 | 0.66 |
| FAT-R | | | |
| volume | 20.61 ± 5.95 | 18.97 ± 5.87 | 0.95 |
| fa | 0.32 ± 0.02 | 0.31 ± 0.03 | 0.85 |
| md | 0.62 ± 0.03 | 0.63 ± 0.03 | 0.79 |
| qa | 0.22 ± 0.02 | 0.24 ± 0.02 | 0.85 |
| ad | 0.83 ± 0.02 | 0.83 ± 0.03 | 0.70 |
| rd | 0.48 ± 0.03 | 0.48 ± 0.03 | 0.83 |
| AF-L | | | |
| volume | 20.40 ± 6.59 | 22.40 ± 6.11 | 0.24 |
| fa | 0.35 ± 0.03 | 0.36 ± 0.02 | 0.24 |
| md | 0.62 ± 0.03 | 0.62 ± 0.03 | 0.79 |
| qa | 0.22 ± 0.02 | 0.21 ± 0.02 | 0.81 |
| ad | 0.84 ± 0.02 | 0.83 ± 0.03 | 0.70 |
| rd | 0.52 ± 0.03 | 0.51 ± 0.03 | 0.48 |
| AF-R | | | |
| volume | 22.40 ± 6.59 | 25.05 ± 6.55 | 0.34 |
| fa | 0.35 ± 0.03 | 0.36 ± 0.03 | 0.30 |
| md | 0.63 ± 0.03 | 0.62 ± 0.03 | 0.91 |
| qa | 0.24 ± 0.02 | 0.22 ± 0.02 | 0.98 |
| ad | 0.84 ± 0.03 | 0.83 ± 0.02 | 0.66 |
| rd | 0.48 ± 0.03 | 0.48 ± 0.03 | 0.87 |

## DISCUSSION

To the best of our knowledge, this is the first study to assess macro and microstructural alterations of the arcuate fasciculus (AF) and frontal aslant tract (FAT) in correlation with cognitive speech tests in PD patients compared to controls using diffusion tractography. Contrary to our hypothesis, our results did not show any statistically significant differences between the overall PD and controls groups in the micro- or macrostructural properties of the tracts, nor in their correlation with verbal fluency measures. However, when we analyze the sex effect, male PD patients exhibited reduced left FAT volume and significantly lower QA in bilateral frontal aslant tract FAT and left AF, indicating a possible fiber damage in males in those tracts.

### Reduced volume of FAT and effect of laterality

Our results showed a statistically significant decrease in the volume of the left FAT in male PD patients compared to controls, while no significant differences were observed in females. Additionally, no significant differences were found in the volume of the AF between groups, regardless of the sex. These results suggest that FAT, rather than AF, may be more directly affected by PD pathology, but this effect may differ by sex, with a potential sex-specific effect and a role for laterality in the disease's impact on brain structures.

The FAT connects the left SMA/pre-SMA to the most posterior part of the inferior frontal gyrus[17] and is involved in language processing, motor planning, and their integration, with left hemisphere connectivity playing a critical role in tasks requiring verbal fluency and executive functions[9,10,18]. Previous studies suggest left-lateralized volumetric differences of FAT in right-handed individuals[19]. Indeed, the left hemisphere's dominance in language systems is a widely recognized concept. Hemispheric asymmetry of the brain is a typical developmental feature influencing cognition, emotion, attention, language, and executive functions[20]. However, it has shown that it can be disrupted in conditions like schizophrenia, dyslexia, and ASD, as well as other psychiatric, neurological, and neurocognitive disorders[21]. Our predominantly right-handed elderly groups align with prior research, showing a reduction in left FAT volume in males, which could indicate the neurodegenerative effects of PD on these critical functions. This reduction may contribute to motor and cognitive impairments that are more pronounced in the left hemisphere.

The absence of a similar effect in female PD patients aligns with the prior literature suggesting the more severe effects of the PD in male individuals with prevalent cognitive

impairment[11,22,23]. The fact that we observed a sex-specific reduction in FAT volume may reflect these underlying differences, with male patients possibly showing greater vulnerability to PD-related damage in FAT.

## Reduced QA and association with white matter integrity

Our results showed a statistically significant decrease in QA bilaterally in the FAT and left AF. The diffusion metrics give indirect information about tissue integrity and diffusion properties. The increase or decrease of these parameters, either alone or in combination, is associated with various conditions and pathologies. QA provides insights into the integrity of white matter tracts by measuring the anisotropic diffusion of water molecules along fiber pathways[14]. Unlike other metrics like FA, QA is less sensitive to noise and partial volume effects, making it a valuable parameter in tractography studies[24]. Decreases in QA are often indicative of reduced white matter integrity and can be associated with various pathological conditions. For instance, studies showed reductions in QA in aging-related changes, neurodegenerative diseases, and other disorders affecting structural connectivity. These reductions may result from changes, such as mild traumatic brain injury, where normalized QA is associated with fiber injury[25].

Tractography has been used to examine the microstructural properties of white matter along specific pathways and to explore the connections between degeneration in these tracts and the severity of language impairment[19,26]. This method has revealed that damage to the left arcuate fasciculus (AF) is linked to deficits in both grammatical comprehension and production[6].

Previously, an analysis of FA values in SMA, prefrontal and anterior cingulate areas revealed a significant decrease in PD patients compared to controls[27]. Consistent with these findings, our results demonstrated a statistically significant decrease in QA bilaterally in the FAT and left AF, further supporting the white matter disruptions in tracts involved in motor and cognitive functions of speech in PD.

## Verbal fluency measures and non-correlating results with QA

Verbal fluency is a cognitive ability that helps retrieve information from memory with two frequent parameters as semantic and phonemic fluency[9]. Semantic fluency is assessed by requesting words from specific categories (e.g., animal names), while phonemic fluency is evaluated by asking for words starting with a particular letter, typically F, A, or S[9]. Our results did not show a correlation between QA and verbal fluency measures. Verbal fluency deficits are among the executive function impairments commonly found in Parkinson's disease (PD) patients and both semantic and phonemic measures have been shown to be sensitive to changes in those patients.

From those two tracts, in general, damage to the AF is associated with impairments in informative speech and related recovery, whereas damage to the FAT is linked to speech fluency[28]. Previous studies have found a correlation between verbal fluency and FAT tractography measures across various subject groups, including both healthy and clinical populations[9]. For example, Catani et al. found that reduced verbal fluency in individuals with the non-fluent type of primary progressive aphasia was related with damage to the FAT, suggesting that microstructural abnormalities in the FAT underpin verbal fluency problems in these patients[19]. Several studies have demonstrated that the FAT is associated with performance on verbal fluency tasks, particularly those that require category-based or phonemic retrieval[29,30]. Specifically, Li et al. found that the lesion load in the FAT was negatively correlated with performance on both semantic (categorical) and phonological fluency tasks in stroke patients, indicating that damage to this tract impairs verbal fluency in these areas[30].

The lack of correlation between our QA measure and verbal fluency scores could be attributed to several factors, both biological and

methodological. One possibility is that the AF and FAT, while crucial to language production, are not the only tracts that take role in verbal fluency performance. The cognitive and neural processes involved in verbal fluency are complex and include many other brain regions and tracts.

Additionally, differences in the methods used for tractography, such as tract segmentation and the choice of regions of interest (ROIs) which was Autotrack in our case, as well as individual variability in brain anatomy, could contribute to the observed discrepancy between QA and verbal fluency measures[19]. For example, poorer performance on complicated verbal memory tasks is associated with extreme left lateralization of the direct long segment of AF, suggesting that while left-lateralized language is fundamental to brain organization, less extreme lateralization may benefit certain cognitive functions.

This suggests that while QA can provide insights into white matter integrity, it may not fully capture the complexity of the neural pathways involved in verbal fluency tasks in Parkinson disease patients.

## Limitations and future research

Unfortunately, due to the retrospective nature of this study, there are some limitations. As the dMRI images were already collected, we did not have the opportunity to further analyze additional structural images for cortical and subcortical analysis. Another point we should emphasize is that we did not have information about whether these patients had a history of prior neurosurgery or traumatic brain injury, which could affect the results. Additionally, the number of participants was limited, and in order to maintain consistency, we decided not to include datasets from other institutions with different scanners, protocols, etc. Another limitation is the absence of longitudinal data, which would have allowed for the assessment of changes over time. Additionally, while we focused on the frontal aslant tract and arcuate fasciculus specifically for this study, other motor and cognitive pathways relevant to Parkinson's disease were not analyzed in depth. Future studies may provide a more comprehensive understanding by examining these additional pathways, which could offer valuable insights into the broader neuroanatomical changes with clinical assessments associated with Parkinson's disease. In summary our findings demonstrate there are microstructural alterations possible identifiers of a fiber in injury in male subjects in comparison to females without a particular correlation between the quantitative anisotropy measures with verbal fluency between PD and control groups.

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