ORIGINAL ARTICLE

White Matter Microstructural Changes in Primary Progressive Aphasia: Insights from Diffusion Tensor Imaging

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Abstract

Purpose: Primary Progressive Aphasia (PPA) is a neurodegenerative syndrome characterized by progressive language impairment. The present study investigated White Matter (WM) microstructural changes in PPA patients and their relationship with language and neuropsychological functions.

Materials and Methods: Diffusion Tensor Imaging (DTI) was used to examine 29 PPA patients and 13 healthy controls, focusing on 18 white matter tracts in both hemispheres.

Results: Significant differences in diffusivity values were observed between PPA patients and controls in multiple tracts, including the Cingulum, Arcuate Fasciculus (AF), Superior Longitudinal Fasciculus (SLF), Inferior Fronto-Occipital Fasciculus (IFOF), Inferior Longitudinal Fasciculus (ILF) bilaterally, as well as the left Uncinate Fasciculus (UF). Correlations between WM integrity and language functions were found in both hemispheres, with the left Cingulum showing positive correlations with various language measures. Notably, right hemisphere tracts (IFOF, ILF, SLF) positively correlated with several language domains, suggesting a potential compensatory role. White matter microstructural changes also correlated with neuropsychological functions (left Cingulum, Left ILF, right IFOF), highlighting PPA's interconnections of language and cognitive domains.

Conclusion: To our knowledge, the present study is the first to identify specific correlations between right hemisphere tracts, language domains, and cognitive functions in PPA patients. Our findings contribute to understanding the neural basis of language impairment in PPA, emphasizing the bilateral nature of language processing in neurodegenerative disorders. The results have implications for diagnosis, prognosis, and treatment planning in PPA, suggesting the need for therapeutic approaches that consider both hemispheres and the interplay between language and broader cognitive functions.

Keywords: Primary Progressive Aphasia; White Matter Microstructure; Diffusion Tensor Imaging; Language Networks; Neuropsychological Function.

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1. Introduction

Primary Progressive Aphasia (PPA) is the second most common neurodegenerative syndrome after Alzheimer's disease in early-onset dementias. A decline in language abilities characterizes this syndrome [1]. Within the first two years of onset, patients typically exhibit noticeable impairments, with language dysfunction being the most prominent feature [2]. PPA patients often show asymmetric damage to the language-dominant hemisphere, resulting in cortical atrophy, hypometabolism, or hypoperfusion [3, 4]. The gradual degeneration of different parts of the language network leads to aphasic symptoms, with the specific pattern of damage varying based on the location of the most significant neuronal loss [1, 4]. While aphasia is the primary cause of dysfunction in PPA patients, other cognitive impairments beyond language deficits are also observed [5, 6]. The co-occurrence of verbal and non-verbal dysfunction may suggest comorbidity, indicating an interactive relationship where non-verbal deficits can impact language abilities and vice versa [7].

White Matter (WM) tracts play a crucial role in connecting cortical hubs within neural networks. Resting-state functional MRI studies demonstrated that atrophy does not affect disrupted connectivity patterns in PPA patients and may instead indicate altered connectivity in the remaining tissue [8, 9]. Research indicates that changes in these WM pathways are valuable for understanding the disintegration of brain networks in neurodegenerative diseases, particularly in PPA [7, 10]. Previous studies have shown that WM changes are more extensive compared to gray matter alterations, emphasizing the vulnerability of brain language networks in such conditions [10].

By assessing white matter integrity using techniques like DTI, researchers have linked white matter disruptions to the progression of language impairments in PPA [11]. DTI evaluates the movement of water in the brain, helping to identify and map WM fiber tracts using a method called tractography. The unique properties of water diffusion in these fibers form the foundation for determining their structural characteristics and integrity [12]. While the exact mechanisms behind WM changes in neurodegenerative diseases are not fully understood, metrics like Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD), and Radial Diffusivity (RD) are commonly used to evaluate microstructural damage in WM, offering valuable insights into disease progression [13].

FA represents the overall direction of water diffusion, showing a greater intensity in organized WM pathways and a lesser degree in Cerebrospinal Fluid (CSF) and disorganized fibers [14]. Meanwhile, MD refers to the uniform degree of water diffusion within the brain tissue. AD and RD, as indicators in DTI, denote damage to axons and myelin, respectively [15].

Numerous studies have investigated differences in WM structural integrity between individuals with PPA and Healthy Controls (HC), particularly focusing on the Left Hemisphere (LH) [16-19]. Multiple studies have also analyzed the corresponding tracts in the Right Hemisphere (RH) [20-22]. While evidence for the involvement of the RH in core language functions mainly comes from gray matter studies, the WM tracts of the RH also play a crucial role in language processing [12]. However, research on the relationship between WM microstructural changes in language tracts and behavioral language measures and neuropsychological impairments in PPA is limited, with a predominant focus on LH tracts [5, 12, 23]. D'Anna *et al.* found a correlation between the Uncinate Fasciculus (UF) and behavioral symptoms [5]. Other studies assessed language, short-term and long-term verbal memory, spatial memory, and attention in the semantic subtype of PPA. They demonstrated the role of the UF and Inferior Longitudinal Fasciculus (ILF) in language and cognitive functions [23]. Furthermore, white matter integrity has been linked to language therapy's effects on PPA [24]. Several studies that included the RH could not find significant associations with language processing [11, 13, 25], while others did find significant associations [12, 26, 27].

Previous studies have reported the importance of white matter tracts such as the Corpus Callosum (CC), Corona Radiata (CR), Inferior Fronto-Occipital Fasciculus (IFOF), Arcuate Fasciculus (AF), ILF, Aslant Tract (AT), Cingulum and UF in supporting language processing [10, 12, 18, 28-30].

Identifying specific white matter tract signatures associated with PPA syndromes can significantly enhance our understanding of the pathophysiology underlying network disintegration relevant to the diseases [12, 19]. Furthermore, white matter changes not only aid in comprehending the disease mechanisms but also show promise in assisting in the diagnosis and monitoring of PPA [10, 24]. On the other hand, as mentioned above, Studies investigating the correlation between WM microstructural alterations and language processing in both cerebral hemispheres are scarce. Similarly, literature is lacking in investigating the correlation between WM microstructural changes and language and neuropsychological functions. To address the gaps, this study aims to investigate three primary aspects. Firstly, it seeks to identify the specific patterns of white matter tract degeneration in both brain hemispheres of individuals with PPA using DTI and various diffusivity metrics. Secondly, the aim is to explore the correlation between language proficiency and white matter microstructural changes in both hemispheres. Finally, the correlation between behavioral and cognitive function and white matter microstructural changes is investigated in both hemispheres.

2. Materials and Methods

2.1. Subjects

This study included 29 individuals diagnosed with PPA and 13 healthy controls matched for age and sex. All participants were recruited from the Yaadmaan Institute for Brain, Cognition, and Memory Studies (IBCMS). A skilled neurologist made the PPA diagnosis following established diagnostic criteria [31]. All participants were native Persian speakers and were right-handed. Before participation, all individuals provided written informed consent, with PPA patients requiring authorization from their legal guardians. All procedures were approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1396.4288; November 9th, 2019). All participants underwent a comprehensive battery of language and neuropsychological evaluations. Tables 1 and 2 summarize the demographic, language, and neuropsychological data for both the PPA and HC groups.

2.2. MRI Acquisition

Structural and DTI imaging were conducted utilizing a Siemens 3 Tesla scanner (Prisma; Siemens Healthcare GmbH, Germany; Production year: 2016) with a 64-channel head coil at the National Brain Mapping Lab (www.nbml.ir). The 3D T1-weighted magnetization-prepared rapid gradient echo (T1-MPRAGE) sequence parameters were as follows: Inversion Time (TI) of 1000 ms, repetition time (TR) of 1,800 ms, acquisition time (TA) of 2.67 min, echo time (TE) of 3.53 ms, voxel size of 1.0 mm × 1.0 mm × 1.0 mm, flip angle of 7°matrix size of 256 × 256 × 160 mm, and an average of 1.

The DTI sequencing protocol had the following specifications: TR of 1100 ms, TE of 105 ms, flip angle of 90°, field of view of 256 × 256, voxel size of 2 × 2 × 2.1 mm, acquisition matrix of 128 ×128 × 60, 60 slices with a 2.1 mm space in between, 2 non-diffusion weighted and 64 non-collinear diffusion gradient directions, b-value of 2000 s/mm^2, and a total scan time of 12 minutes and 19 seconds.

2.3. MRI Processing

2.3.1. Quality Control

The quality of analyzed and raw DWI data was evaluated. To ensure the absence of any possible vibration/motion evidence, signal loss, macroscopic artifacts, head tilt, and positioning issues, DWI image information including the voxel sizes, image matrix, directions, and the number of B0 images was checked while examining the raw data. Similarly, the analyzed data were scrutinized, checking the tensor orientation, and identifying the outlier scans. In the subsequent stage, the scans identified as

Outliers were removed based on the corresponding outlier profile maps found in the *.mat DWI files and residual graph.

2.3.2. Preprocessing

The DTI data processing involved several steps using ExploreDTI software (v4.8.6). Initially, the data was converted to the NIFTI format, with the two B0 images positioned as the first volumes of the DWI nii file. Subsequently, the B-matrix was generated utilizing the *.b_{val} and *.b_{vec} files. A comprehensive

Table 1. Demographic information of PPA and HC groups

	PPA (n= 29)		Control (n=13)	
	range	**mean±SD**	**range**	**mean±SD**
Age (y)	48-79	63.3448±7.56059	49-79	58.08±8.732
Age at onset (y)	46-75	59.3793±7.51386	49-79	58.08±8.732
Symptoms duration (y)	1-11	3.9655±2.65226		
Education	4-22	12.9310±4.91124	9-22	15.1538±3.46060
Gender (f/m)		20/9		10/3
Handedness		Right		Right

PPA= Primary Progressive Aphasia; HC= healthy controls

Table 2. Language and neuropsychological features of PPA and HC groups

Dependent variable	**HC**		**PPA**	
	mean	**SD**	**mean**	**SD**
Language features				
P-WAB AQ	98.33	1.3635	64.7203	22.0248
Fluency	126.25	19.612	43.5587	19.9514
PNT	50.00	.000	32.2413	16.3808
Single word comprehension	100.00	.000	65.3448	28.7318
Auditory comprehension	51.00	.000	34.0689	13.9410
Reading comprehension	38.00	.000	18.8620	12.0910
Oral reading	100.00	.000	61.8965	26.4485
Repetition	20.00	.000	13.3448	4.9009
Automatic speech	8.00	.000	4.96	4.4859
Writing	20.00	.000	7.92	7.2279
Neuropsychological features				
MMSE	29.77	0.439	12.3448	7.9967
P-NPI	-	-	9.76	5.390
P-DAD	100	0.00	60.9672	25.5760
BADL	23	0.00	12.4137	4.5475
IADL	17	0.00	10.5172	6.1737
CDT[a]	1.15	0.376	4.9655	1.2095
P-FAB	17.62	0.650	6.7241	3.3155
TMT-A[a]	31.159	6.905	129.6428	65.7742
FDST	10.46	2.537	3.6206	2.1282
P-AVLT learning	57.23	10.264	18.5217	12.4274
P-AVLT delayed recall	11.92	2.253	3.9565	3.5094

[a]= "Higher scores indicate poorer performance or a greater degree of abnormality; SD= standard deviation; HC= healthy control; PPA= Primary Progressive Aphasia; P-WAB AQ1= Bedside version of Persian Western Aphasia Battery; PNT= Persian Picture Naming Test; MMSE= Mini-Mental State Examination; P-NPI= Persian version of neuropsychiatric inventory; P-DAD= Persian version of Disability Assessment for Dementia; BADL= Basic Activities of Daily Living; IADL= Activities of Daily Living; CDT= clock drawing test; P-FAB= Persian version of frontal assessment battery; TMT-A= trial making test-part A; FDST= forward digit span test; P-AVLT= Persian version of auditory verbal learning test.

correction process was then conducted on the DWI data to address various artifacts and distortions. This correction encompassed rectifying the Gibbs artifacts, participant motion effects, tissue susceptibility-induced distortions, and eddy current-induced distortions. Specifically, motion correction involved

aligning the DWI volumes to the B0 image through affine transformation, with a corresponding adjustment of the b-matrix to maintain principal directions [32]. Furthermore, to correct tissue susceptibility distortions, a non-rigid transformation was applied to T1-weighted images, allowing deformations solely in the phase encoding direction.

To accomplish this, two steps are carried out (1. Setting-SM/EC/EPI correction- yes to do the EPI correction; 2. Plugin- correct for subject motion and EC/EPI correction). The final output consists of two files named “trafo” and “native.” Only corrections have been applied to the “native” file, while the “trafo” file has also been registered to the T1 image in addition to those corrections.

2.3.3. Tractography

The White Matter (WM) tract of the entire brain was reconstructed for each participant through linear interpolation, utilizing a seed fractional anisotropy threshold of 0.2, a seed point resolution of 1 × 1 × 1 mm^3, and an angle threshold of 30°.

Based on previous research [10, 19, 23, 28, 33-41], 18 white matter fiber bundles were considered. These included bilateral Arcuate Fasciculus (right and left AF), bilateral Aslant tract (right and left AT), bilateral Corona Radiata (right and left CR), bilateral dorsal cingulum (right and left), Fornix, bilateral Uncinate Fasciculus (right and left UF), bilateral Inferior Fronto-Occipital Fasciculus (right and left IFOF), bilateral Inferior Longitudinal Fasciculus (right and left ILF), bilateral Superior Longitudinal Fasciculus (right and left SLF), and the Corpus Callosum (CC).

The identification of 18 potential fiber bundles involved the application of the atlas-based track segmentation module within ExploreDTI. Initially, a single-subject template from the HC group was selected based on the quality of DWI and T1-weighted images. Subsequently, Regions Of Interest (ROI) were outlined on the directionally encoded FA map of the single-subject template for each fiber pathway. These ROIs, delineated under the guidance of an expert neuroanatomist following established protocols, comprised AND or NOT maps and were then utilized for automated atlas-based segmentation [42, 43]. Figures 1 and 2 illustrate the eighteen candidate tracts of HC and PPA groups.

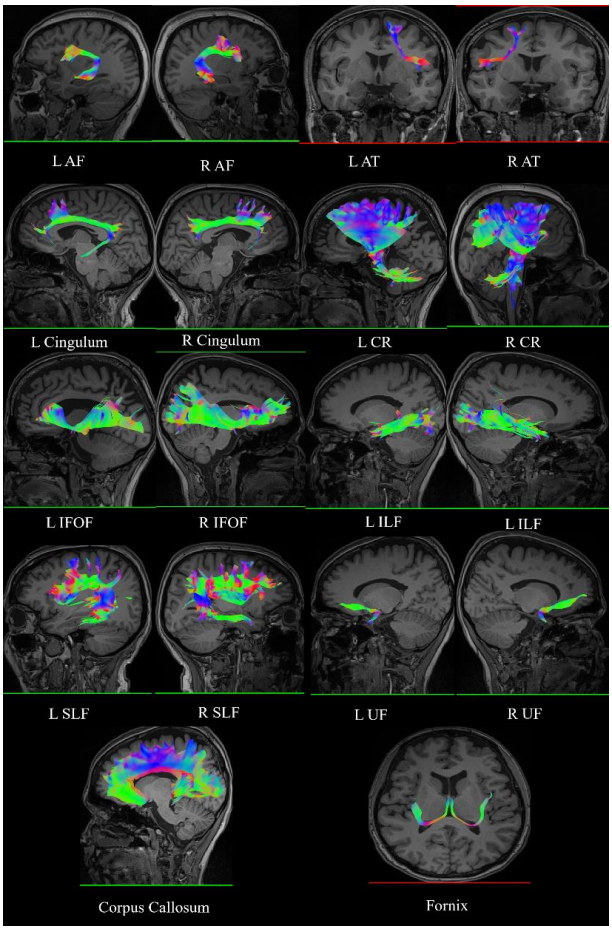

Figure 1. Reconstructions of white matter tracts in control individuals. The 18 white matter bundles are superimposed onto the subject’s fractional anisotropy map. R= right; L = left; AF= Arcuate fasciculus; AT= Aslant Tract; IFOF= Inferior Fronto-Occipital Fasciculus; CR= Corona Radiata; ILF= Inferior Longitudinal Fasciculus

After defining ROIs and adjusting a single-subject template to each subject's space through a rigid transformation (6 degrees of freedom). Subsequently, the ROIs were aligned with each subject's space. The aforementioned process was carried out using the "Automated atlas-based tractography" toolbox from ExploreDTI to identify potential fiber pathways based on the adjusted ROIs for each subject. The final step included estimating the mean values for various parameters such as MD, FA, RD, AD, and the Number Of Tracts (NOT) for each distinct tract.

2.4. Statistical Analysis

The statistical analyses were conducted using SPSS software (version 25). To assess the normal distribution assumption, Q-Q plots, Shapiro-Wilk, and Kolmogorov-Smirnov tests were employed. Mann-

Whitney U tests (for non-parametric data) and Independent-sample t-tests (for parametric data) were utilized to compare group differences between control and PPA groups in FA, MD, AD, RD, and NOT of the different tracts of interest. To describe the strength and direction of the linear relationship between the language and neuropsychological cognitive features and tract-specific measurements, Spearman's Rho for non-parametric data and Pearson analysis for parametric data were used. Based on the Bonferroni correction method (Family-wise error rate (0.05 divided by number of variables (40)), the significance level was set at p-value ≤0.00125. It is important to note that the significance level for all reported data is p≤ 0.00125.

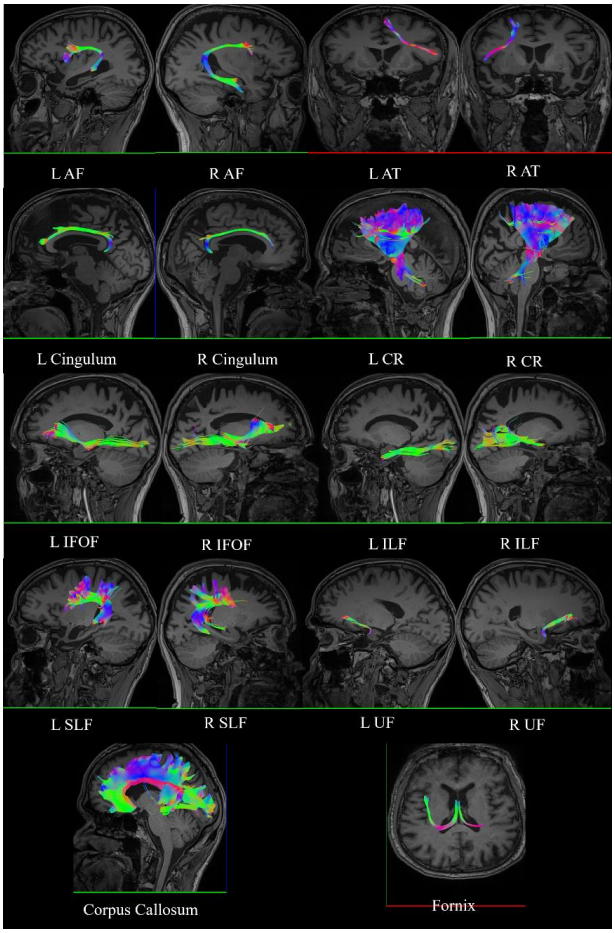

Figure 2. Reconstructions of white matter tracts in PPA patients. The 18 white matter bundles are superimposed onto the subject's fractional anisotropy map. R= right; L = left; AF= Arcuate Fasciculus; AT= Aslant Tract; IFOF= Inferior Fronto-Occipital Fasciculus; CR= Corona Radiata; ILF= Inferior Longitudinal Fasciculus

3. Results

3.1. Diffusivity Values of HC and PPA Groups

Patients with PPA exhibited significantly lower FA and NOT in the CC (FA, p=0.000; NOT, p=0.000), Fornix (FA, p=0.000; NOT, p=0.000), and left IFOF (FA, p=0.000003; NOT, p=0.000) compared to the HC group. Also, CC and left IFOF showed remarkably higher MD (CC, p=0.000; l-IFOF, p=0.000), and RD (CC, p=0.00002; l-IFOF, p=0.000087) values than the HC group. Additionally, the AD value of CC significantly differed from the HC group (p=0.000). Furthermore, the left SLF (FA, p=0.000013; MD, p=0.00011; AD, p=0.0004; RD, p=0.00001), left AF (FA, p=0.000146; MD, p=0.000008; AD, p=0.0001; RD, p=0.000), and left UF (FA, p=0.0001; MD, p=0.000022; AD, p=0.0001; RD, p=0.000099), of PPA patients exhibited significantly lower FA and higher MD, AD, and RD compared to the HC group. The left ILF of HC individuals displayed significantly higher FA (p=0.000005) and lower AD (p=0.000264) compared to PPA patients. Left cingulum RD (p=0.000016) and MD (p=0.000423) values showed a meaningful increase compared with HC. Additionally, the left cingulum FA value was crucially lower in the PPA group compared to HC individuals (p=0.000005) (Table 3).

In the right hemisphere, AF of the PPA group showed significantly higher MD (p=0.000007), AD (p=0.00009), and RD (p=0.000033) relative to HC individuals. Furthermore, FA (r-Cingulum, p=0.000008; r-IFOF, p=0.00005) and NOT (r-Cingulum, p=0.0005; r-IFOF, p=0.000) values of right Cingulum and right IFOF displayed a significant decrease in comparison with the HC group. On the contrary, RD values of the right IFOF (p=0.001) and right Cingulum (p=0.000017) showed a remarkable increase in comparison with the HC individuals. Patients with PPA, AD (p=0.001), and NOT (p=0.000) values of the right SLF, exhibited significant alterations compared to the HC group. Furthermore, the right ILF of PPA patients demonstrated a significantly higher RD (p=0.000001) and the right CR (p=0.000) had significantly lower NOT values in comparison with HC individuals (Table 3).

Table 3. Differences in diffusivity values between HC and PPA groups

Tract	HC		PPA				Other significant diffusivity values
	FA	MD	FA		MD		
	Mean±SD	Mean±SD	Mean±SD	Sig. difference with HC	Mean±SD	Sig. difference with HC.	
Left side							
AF	0.4972±0.023	6.0E-4±5.2E-5	0.4431±0.04	*	7.0E-4±5.1E-5	*	AD, RD[1]
AT	0.4223±0.031	6.1E-4±3.6E-5	0.3836±0.05	n.s.	6.5E-4±5.7E-5	n.s.	
Cingulum	0.5182±0.029	6.3E-4±1.9E-5	0.4288±0.056	*	7.1E-4±7.1E-5	n.s.	RD
CR	0.5155±0.028	6.3E-4±2.0E-5	0.5101±0.024	n.s.	7.1E-4±1.2E-4	*[1]	
IFOF	0.5093±0.02	7.1E-4±3.5E-5	0.4369±0.035	*	8.1E-4±9.7E-5	*[1]	RD, NOT
ILF	0.4612±0.017	7.1E-4±3.9E-5	0.4078±0.034	*	7.8E-4±2.0E-4	n.s.	AD,
SLF	0.4945±0.019	6.2E-4±3.1E-5	0.4338±0.041	*	6.7E-5±6.8E-4	*	RD,
UF	0.4040±0.029	6.9E-4±3.3E-5	0.3607±0.037	*	7.6E-4±5.0E-5	*	AD, RD,
Both side							
CC	0.5448±0.018	7.1E-4±2.8E-5	0.4912±0.028	*	1.2E-3±1.5E-3	*	AD[1], RD, NOT[1]
Fornix	0.3711±0.02	1.2E-3±1.0E-4	0.3221±0.026	*	1.4E-3±1.0E-4	n.s.	NOT[1]
Right side							
AF	0.4725±0.021	6.1E-4±9.9E-4	0.4325±0.04	n.s.	7.1E-4±5.5E-5	*	AD, RD,
AT	0.4109±0.053	6.1E-4±4.3E-5	0.3729±0.04	n.s.	6.6E-4±5.6E-5	n.s.	
Cingulum	0.5041±0.046	6.1E-4±5.0E-5	0.4244±0.044	*	6.9E-4±7.0E-5	n.s.	RD, NOT
CR	0.4764±0.017	6.4E-4±2.6E-5	0.4811±0.022	n.s.	6.8E-4±5.4E-5	n.s.	
IFOF	0.4706±0.017	6.9E-4±3.0E-5	0.4266±0.032	*	7.4E-4±7.7E-5	n.s.	NOT[1]
ILF	0.4499±0.023	7.0E-4±2.5E-5	0.4025±0.031	*	7.9E-4±4.9E-5	*	RD
SLF	0.4638±0.021	6.0E-4±5.1E-5	0.4229±0.036	*	6.7E-4±6.2E-5	n.s.	AD, NOT
UF	0.3911±0.022	6.7E-4±5.2E-5	0.3717±0.041	n.s.	7.6E-4±8.9E-5	n.s.	

[1] = analyzed with the Mann-Whitny U test. Other comparisons were analyzed using independent sample t-tests. The mean ± standard deviation (SD) values of FA and MD measurements for the 18 white matter tracts were compared between the PPA and HC groups. Other significant diffusivity values are indicated in the last column. Statistical significance between the measurements of the two groups is indicated by p-values, which are adjusted using a significance threshold of ≤ 0.00125 while controlling the Family-Wise Error Rate (FWER). HC= healthy control; PPA= primary progressive aphasia; AF= Arcuate fasciculus; CC= corpus callosum; CR= corona radiata; IFOF= inferior fronto-occipital fasciculus; ILF= inferior longitudinal fasciculus; SLF= superior longitudinal fasciculus; UF= uncinate fasciculus; FA= fractional anisotropy; MD= mean diffusivity; AD= axial diffusivity; RD= radial diffusivity; NOT= number of tracts; n.s.=non-significant.

3.2. White Matter Diffusivity Values Correlation with Language Features of PPA Patients

Table 4, presented the significant correlations of diffusivity values of the above-mentioned left and right hemisphere tracts, and CC tracts with language variables within the PPA patients. Both positive and negative correlations were found among DTI parameters and language factors. The FA and RD values of bilateral CC had a positive and negative correlation with oral reading Western aphasia battery (P-WAB-AQ1) (FA, p=.001; RD, p=0.001), single word comprehension (FA, $p=157x10^{-3}$; RD, $p=4x10^{-4}$), Auditory comprehension (FA, p=.001; RD, $p=19x10^{-4}$), oral reading (FA, $p=639x10^{-3}$; RD, $p=39x10^{-4}$), and writing (FA, p=.001; RD, $p=346x10^{-3}$), respectively.

3.2.1. Left Hemisphere

FA value of the left Cingulum had a positive correlation with the P-WAB-AQ1 ($p=204x10^{-3}$), auditory comprehension (p=0.001), single-word comprehension ($p=157x10^{-3}$), reading comprehension (p=0.001), oral reading ($p=422x10^{-3}$), automatic speech ($p=331x10^{-3}$), writing (p=.001), and repetition ($p=163x10^{-3}$) criteria. MD and RD values of the current tract had a negative correlation with P-WAB-AQ1 (MD, $p=121x10^{-3}$; RD, $p=47x10^{-4}$), Persian picture naming test (PNT) (MD, $p=x10^{-3}$; RD, $p=203x10^{-3}$), auditory comprehension (MD, $p=46x10^{-3}$; RD, $p=18x10^{-4}$), single-word comprehension (MD, $p=16x10^{-4}$; RD, $p=7x10^{-5}$), repetition (MD, p=0.001;

RD, p=477x10^{-3}) and oral reading (MD, p=44x10^{-4}; RD, p=25x10^{-4}) scales. Moreover, the RD value of the left CR exhibited a negative correlation with oral reading (p=0.001), and repetition (p=0.001). Additionally, the MD value of left CR was negatively correlated with fluency (p=001). Auditory comprehension (p=0.001), single-word comprehension (p=447x10^{-3}), reading comprehension (p=55x10^{-3}), and oral reading (p=263x10^{-3}) were negatively correlated with the RD value of left ILF. The MD and RD values of the SLF exhibited negative correlations with P-WAB AQ1 (MD, p=.001; RD, p=0.001), single word comprehension (MD, p= 337xx10^{-3}; RD, p= 291x10^{-3}), auditory comprehension (MD, p=411x10^{-3}; RD, p= 294x10^{-3}), and oral reading (MD, p= 0.001; RD, p= 0.001). Furthermore, the NOT value of UF positively correlated with writing (p=0.001).

3.2.2. Right Hemisphere

The P-WAB-AQ1 score expressed a positive correlation with the FA value of IFOF (p=443x10^{-3}) and SLF (p=0.001) tracts. Moreover, auditory comprehension (FA, p=196x10^{-3}; RD, p=256x10^{-3}), single-word comprehension (FA, p=0.001; RD, p=206x10^{-3}), oral reading (FA, p=0.001; RD, p=0.001), and P-WAB-AQ1 (FA, p=0.001; RD, p=0.001), had respectively positive and negative correlations with FA and RD values of the SLF tract. The FA values of ILF and IFOF tracts were positively correlated with single-word comprehension (ILF, p=238x10^{-3}; IFOF, p=9x10^{-5}), PNT (ILF, p=0.001; IFOF, p=1x10^{-4}), and oral reading (ILF, p=0.001; IFOF, p=39x10^{-4}) scores. Furthermore, reading comprehension (p=0.001), P-WAB-AQ1 (443x10^{-3}), and repetition (p=183x10^{-3}) displayed a positive correlation with FA values of the IFOF tract. However, MD values of the CR tract were negatively correlated with P-WAB-AQ1 (p=0.001), single-word comprehension (p=251x10^{-3}), auditory comprehension (p=311x10^{-3}), oral reading (p=245x10^{-3}) and repetition (p=0.001). The FA value of the AT tract demonstrated a positive correlation with single-word comprehension (p=0.001), auditory comprehension (p=0.001), and oral reading scores (p=0.001). Additionally, PNT (MD, p=222xx10^{-3}; RD, p= 0.001), single-word comprehension (MD, p=185x10^{-3}; RD, p= 172x10^{-3}), auditory comprehension (MD, p=0.001; RD, p= 0.001), and reading comprehension (MD, p=0.001; RD, p= 0.001) criteria negatively correlated with MD and RD values of AF (Table 4).

3.3. White Matter Diffusivity Values Correlation with Neuropsychological Features

Table 5, presented the correlation between WM diffusivity values and neuropsychological features. The forward digit span test (FDST) negatively correlated with the AD value of the right SLF (p=406x10^{-3}). Furthermore, basic activity of daily living (BADL) criteria exhibited a negative correlation with MD values of CC (p=478x10^{-3}) and left IFOF (p=0.001). The MD value of the right SLF (p=75x10^{-3}) and right AF (p=0.001) negatively correlated with the clock drawing test (CDT) (Table 5). The AD value of The Persian version of frontal assessment battery (P-FAB) implied a negative correlation with the MD value of CC (p=312x10^{-3}) (Figure 3). Persian version of Disability Assessment for Dementia (P-DAD) negatively correlated with Left CC MD value (p=36x10^{-4}). Left Cingulum FA values showed a positive correlation with the Mini-Mental State Examination (MMSE) scales (p=359x10^{-3}) and the P-DAD (p=0.001) (Figure 3). Conversely, the Neuropsychiatric Inventory (P-NPI) scale negatively correlated with the FA value of the left ILF tract (p=0.001) (Figure 3). Furthermore, the FA value of the right IFOF showed a positive correlation with P-DAD (p=0.001), MMSE (p=0.001), and P-FAB (p=26x10^{-4}), while exhibiting a negative correlation with CDT scores (p=0.001) (Figure 4).

4. Discussion

The current research investigated the alterations in the microstructure of WM tracts in patients with PPA comparing with HC individuals. Moreover, the study explored the relationships between these microstructural changes in WM tracts and language as well as neuropsychological processing in PPA across both hemispheres. The diffusivity measurements of various WM tracts in PPA patients revealed significant differences when compared to HC individuals. Additionally, significant correlations were noted between the diffusivity measurements of

Table 4. Significant correlations between language variables and diffusivity values in PPA patients

Tract	Language variable									
	P-WAB AQ1	Fluency	PNT[1]	Single word comprehension	Auditory comprehension	Reading comprehension[1]	Oral reading	Repetition	Automatic speech[1]	writing
					Left side					
AF		FA (.599*) (p=.001)								
AT										
Cingulum	FA (.646*) ($p=204x10^{-3}$) MD (-.663*) ($p=121x10^{-3}$) RD (-.691*) ($p=47x10^{-3}$)	MD (-.631*) ($p=321x10^{-3}$) RD (-.646*) ($p=203x10^{-3}$)		FA (.644*) ($p=22x10^{-3}$) MD (-.719*) ($p=16x10^{-3}$) RD (-.738*) ($p=7x10^{-5}$)	FA (.588*) (p=.001) MD (-.692*) ($p=46x10^{-3}$) RD (-.717*) ($p=18x10^{-4}$)	FA (.612*) (p=.001) RD (-.606*) (p=.001)	FA (.621*) ($p=422x10^{-3}$) MD (-.693*) ($p=44x10^{-4}$) RD (-.708*) ($p=25x10^{-4}$)	FA (.653*) ($p=163x10^{-3}$) MD (-.572*) (p=.001) RD (-.616*) ($p=477x10^{-3}$)	FA (.630*) ($p=331x10^{-3}$)	FA (.609*) (p=.001)
CR		MD (-.591*) (p=.001)					RD (-.587*) (p=.001)	RD (-.593*) (p=.001)		
IFOF				MD[1] (-.662*) ($p=124x10^{-3}$) RD (-.694*) ($p=43x10^{-4}$)	MD (-.590*) (p=.001) RD (-.670*) ($p=96x10^{-4}$)		RD (-.645*) ($p=208x10^{-3}$)	RD (-.580*) (p=.001)		MD (-.574*) (p=.001) RD (-.572*) (p=.001)
ILF				FA (.625*) ($p=379x10^{-3}$) RD (-.619*) ($p=447x10^{-3}$)	FA (.603*) (p=.001) RD (-.613*) (p=.001)	FA (.643*) ($p=222x10^{-3}$) RD (-.687*) ($p=55x10^{-4}$)	FA (.595*) (p=.001) RD (-.638*) ($p=263x10^{-3}$)			
SLF	MD (-.589*) (p=.001) RD (-.600) (p=.001)			MD (-.629*) ($p=337x10^{-3}$) RD (-.634*) ($p=291x10^{-3}$)	MD (-.622*) ($p=411x10^{-3}$) RD (-.634*) ($p=294x10^{-3}$)		MD (-.590*) (p=.001) RD (-.584*) (p=.001)			
UF										NOT[1] (.594*) (p=.001)
					Both side					
CC	FA (.596*) (p=.001) RD (-.618*) (p=.001)			FA (.644*) ($p=22x10^{-3}$) MD (-.676*) ($p=109x10^{-3}$) RD (-.760*) ($p=4x10^{-5}$)	FA (.604*) (.001) MD (-.622*) (p=.001) RD (-.725*) ($p=19x10^{-4}$)		FA (.639*) ($p=338x10^{-3}$) MD (.586*) (p=.001) RD (-.706*) ($p=39x10^{-4}$)	FA (.620*) (p=.001)	FA (.593*) (p=.001)	FA (.583*) (p=.001) MD (-.603*) (p=.001) RD (-.638*) ($p=346x10^{-3}$)
Fornix										
					Right side					
AF			MD (-.670*) ($p=222x10^{-3}$) RD (-.645*) (p=.001)	MD (-.680*) ($p=185x10^{-3}$) RD (-.682*) ($p=172x10^{-3}$)	FA (.607*) (p=.001) MD (-.609*) (p=.001) RD (-.635*) (p=.001)	MD (-.631*) (p=.001) RD (-.601*) (p=.001)	RD (-.605*) (p=.001)			
AT	MD (-.665*) (p=.001) RD (-.661*) (p=.001)			FA (.650*) (p=.001) MD (-.765*) ($p=53x10^{-4}$) RD (-.753*) ($p=81x10^{-4}$)	FA (.653*) (p=.001) MD (-.746*) ($p=103x10^{-3}$) RD (-.734*) ($p=151x10^{-3}$)		FA (.664*) (p=.001) MD (-.711*) ($p=3x10^{-3}$) RD (-.708*) ($p=327x10^{-3}$)		FA (.656*) (p=.001)	
Cingulum	RD (-.665*) ($p=208x10^{-3}$)			MD (-.718*) ($p=37x10^{-4}$) RD (-.788*) ($p=2x10^{-5}$)	MD (-.695*) ($p=82x10^{-4}$) AD (-.609*) (p=.001) RD (-.744*) ($p=13x10^{-3}$)		MD (-.658*) ($p=256x10^{-3}$) RD (-.777*) ($p=3x10^{-5}$)	RD (-.641*) ($p=421x10^{-3}$)		RD (-.638*) ($p=460x10^{-3}$)

CR	MD (-.579*) (p=.001)			MD (-.639*) ($p=251x10^{-3}$) AD (-.580*) (p=.001)	MD (-.632*) ($p=311x10^{-3}$)		MD (-.640*) ($p=245x10^{-3}$) AD (-.576*) (p=.001)	MD (-.592*) (p=.001)
IFOF	FA (.620*) ($p=433x10^{-3}$)	AD (-.575*) (p=.001)	FA (.731*) ($p=110^{-4}$)	FA (.733*) ($p=9x10^{-5}$) RD[1] (-.654*) ($p=162x10^{-3}$)	FA (.698*) ($p=36x10^{-3}$)	FA (.582*) (p=.001) RD[1] (-.606*) (p=.001)	FA (.696*) ($p=39x10^{-4}$)	FA (.650*) ($p=183x10^{-3}$)
ILF			FA (.574*) (p=.001) MD (-.586*) (p=.001)	FA (.641*) ($p=238x10^{-3}$) MD (-.645*) ($p=213x10^{-3}$) RD (-.645*) ($p=160x10^{-3}$)	FA (.591*) (p=.001) RD (-.610*) (p=.001)		FA (.582*) (p=.001) RD (-.581*) (.001)	
SLF	FA (.592*) (p=.001) RD(-.585*) (p=.001)			FA (.583*) (p=.001) RD (-.646*) ($p=206x10^{-3}$)	FA (.647) ($p=196x10^{-3}$) RD (-.638*) ($p=256x10^{-3}$)		FA (.580*) (p=.001) RD (-.606*) (p=.001)	RD (-.606*) (p=.001)
UF				FA (.650*) (p=.001)	FA (.674*) (p=.001) MD (-.664*) (p=.001) RD (-.679*) (p=.001)		MD (-.679*) (p=.001) RD (-.658*) (p=.001)	MD (-.667*) (p=.001)

The correlation of diffusivity values of the 18 white matter tracts and language variables. [1] analyzed with Spearmen's Rho; The p-values indicate statistically significant correlations between these variables. * indicate significant corrected values with the family-wise error rate; significant level ≤0.00125; the values in parentheses represent R values; PPA= Primary Progressive Aphasia; P-WAB AQ1= Bedside version of Persian Western Aphasia Battery; PNT= Persian Picture Naming Test; AF= Arcuate fasciculus; CC= corpus callosum; CR= corona radiata; IFOF= inferior fronto-occipital fasciculus; ILF= inferior longitudinal fasciculus; SLF= superior longitudinal fasciculus; UF= uncinate fasciculus; FA= fractional anisotropy; MD= mean diffusivity; RD= radial diffusivity; AD= axial diffusivity; NOT= number of tracts

Table 5. Significant correlations between neuropsychological variables and diffusivity values in PPA patients

tract	**Behavioral and cognitive variable**							
	MMSE	**P-NPI**	**P-DAD**	**BADL[1]**	**IADL[1]**	**CDT**	**P-FAB**	**TMA**
Left side								
AF								
AT								
Cingulum	FA (.627*) ($p=359x10^{-3}$) MD (-.638*) ($p=259x10^{-3}$) RD (-.670*) ($p=97x10^{-4}$)		FA (.587*) (p=.001) MD (-.577*) (p=.001) RD (-.586*) (p=.001)		FA (.605*) (p=.001)		FA (.717*) ($p=18x10^{-4}$) MD (-.676*) ($p=79x10^{-4}$) RD (-.666*) ($p=110x10^{-3}$)	

ILF	FA (.643*) ($p=225x10^{-3}$)	FA (-.598*) (p=.001)					
SLF							RD (-.580*) (p=.001)
UF	MD (-.628*) (p=.001)		MD (-.612*) (p=.001)				
				Both side			
CC	RD (-.604*) (p=.001)		MD (-.708*) ($p=36x10^{-4}$) RD (-.673*) ($p=119x10^{-3}$)	MD (-.626*) ($p=36x10^{-4}$) RD (-.588*) (p=.001)	MD (-.603*) (p=.0001) RD (-.604) (p=.001)		FA (.629*) ($p=438x10^{-3}$) MD (-.641*) ($p=312x10^{-3}$) RD (-.729*) ($p=16x10^{-4}$)
Fornix							
				Right side			
AF		MD (.732*) ($p=32x10^{-4}$) RD (.739*) ($p=24x10^{-4}$)	MD (-.671*) ($p=243x10^{-3}$) AD (-.614*) (p=.001) MD (-.606*) (p=.001)	MD (-.611*) (p=.001) AD (-.642*) (p=.001)		MD (.629*) (p=.001) MD (.617*) (p=.001)	FA (.640*) (p=.001) MD (-.739*) ($p=24x10^{-4}$) RD (-.742*) ($p=22x10^{-4}$)
AT			MD (-.652*) (p=.001) AD (-.649*) (p=.001)	MD (-.653*) (p=.001)			
Cingulum			MD (-.701*) ($p=66x10^{-4}$) RD (-.717*) ($p=38x10^{-4}$)	MD (-.723*) ($p=30x10^{-4}$) RD (-.743*) ($p=14x10^{-4}$)	RD (-.636*) ($p=476x10^{-3}$)		FA (.607*) (p=.001) RD (-.710*) ($p=49x10^{-4}$)
CR							MD (-.579*) (p=.001)
IFOF	FA (.591*) (p=.001) RD^1 (-.657*) ($p=148x10^{-3}$)	FA (-.717*) ($p=18x10^{-4}$)	FA (.577*) (p=.001) RD^1 (-.653*) ($p=164x10^{-3}$)	RD^1 (-.631*) ($p=321x10^{-3}$)		FA (-.584*) (p=.001) RD^1 (.651*) ($p=178x10^{-3}$)	FA (.707*) ($p=26x10^{-4}$) RD^1 (-.630*) ($p=330x10^{-3}$)
ILF	FA (.580*) (p=.001)	FA (-.649*) ($p=188x10^{-3}$) MD (.732*) ($p=1x10^{-4}$) RD (.708*) ($p=25x10^{-4}$)		MD (-.601*) (p=.001) MD (-.600*) (p=.001)			FA (.652*) ($p=171x10^{-3}$)

SLF	RD (-.586*) (p=.001)	MD (-.662*) ($p=123x10^{-3}$) AD (-.576*) (p=.001)	MD (-.604*) (p=.001)	MD (.677*) ($p=75x10^{-4}$)	MD (-.579*) (p=.001) RD (-.609*) (p=.001)	AD (-.642*) ($p=406x10^{-3}$)
UF						

The correlation of diffusivity values of the 18 white matter tracts and language variables. [1] analyzed with Spearmen's Rho; The p-values indicate statistically significant correlations between these variables. * indicate significant corrected values with the family-wise error rate; significant level ≤0.00125; the values in parentheses represent R values; MMSE= Mini-Mental State Examination; P-DAD= Persian version of Disability Assessment for Dementia; BADL= basic activities of daily living; IADL= Instrumental activities of daily living; CDT= Clock Drawing Test; P-FAB= Persian version of the Frontal Assessment Battery; TMT-A= Trial Making Test-A; FDST= Forward Digit Span Test; P-AVLT= Persian version of the Auditory Verbal Learning; ; AF= Arcuate fasciculus; AT= aslant tract; CC= corpus callosum; CR= corona radiata; IFOF= inferior fronto-occipital fasciculus; ILF= inferior longitudinal fasciculus; SLF= superior longitudinal fasciculus; UF= uncinate fasciculus; FA= fractional anisotropy; MD= mean diffusivity; RD= radial diffusivity; AD= axial diffusivity; significant level for uncorrected values≤0.05; significant level for corrected values≤0.00125.

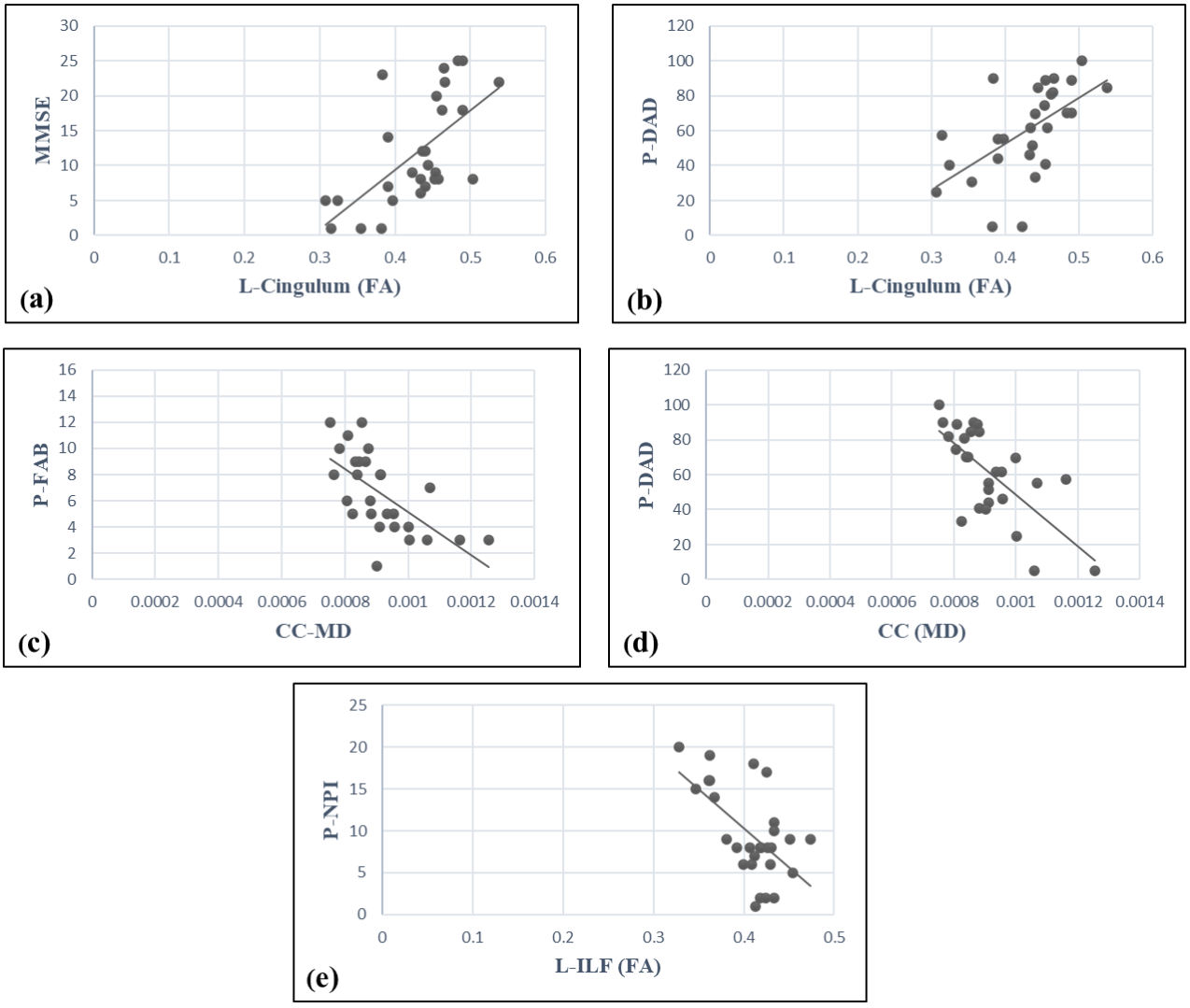

Figure 3. Correlation between left hemisphere tracts and cognitive/behavioral evaluations. (a) positive correlation between MMSE and FA value of left Cingulum (R=0.627, $p=359x10^{-3}$); (b) positive correlation between P-DAD and FA value of left Cingulum (R=0.587, p=0.001); (c) negative correlation between MD value of CC and P-FAB (R=-0.641, $p=312x10^{-3}$); (d) negative correlation between MD value of CC and P-DAD (R= -0.708, $p=36x10^{-4}$); (e) negative correlation between FA value of left ILF and P-NPI (R=-0.598, p=0.001). L = left; R= right; CR= Corona Radiata; CC= corpus callosum; ILF= Inferior Longitudinal Fasciculus

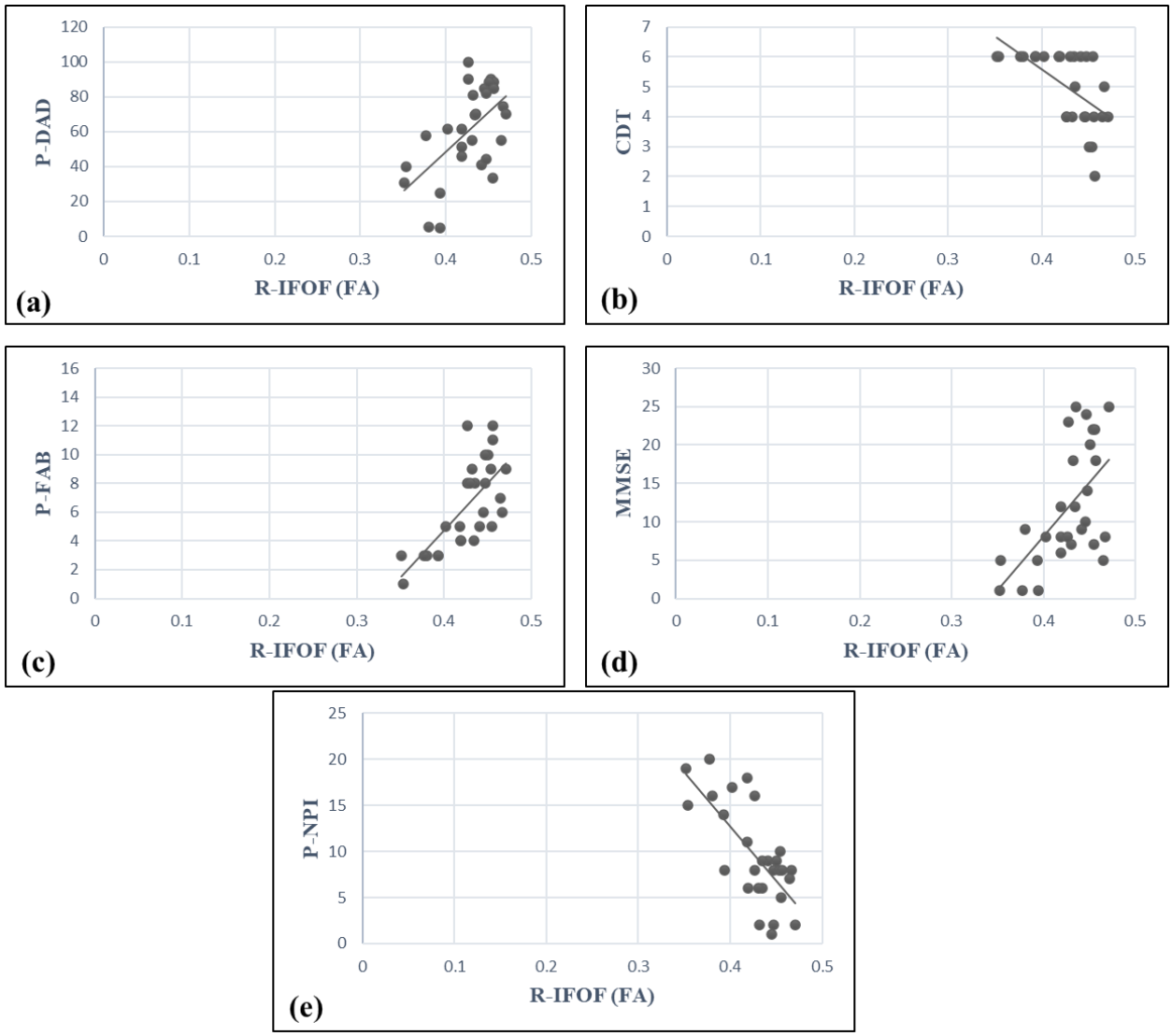

Figure 4. Correlation between FA value of right IFOF and cognitive/behavioral evaluations. (a) positive correlation between P-DAD and FA value of IFOF (R=0.577, p=0.001); (b) negative correlation between CDT and FA value of right IFOF (R=-0.584, p=0.001); (c) positive correlation between FA value of right IFOF and P-FAB (R=0.707, $p=26x10^{-4}$); (d) positive correlation between FA value of right IFOF and MMSE (R=0.591, p=0.001); (e) negative correlation between FA value of right IFOF and P-NPI (R=0.717, $p=18x10^{-4}$); R= right; IFOF= Inferior Fronto-Occipital Fasciculus

these tracts and language characteristics in PPA patients, with various language factors showing both positive and negative associations with DTI parameters. Furthermore, relationships between diffusivity measurements and neuropsychological aspects within PPA patients were identified, highlighting connections between WM microstructural changes and cognitive functioning.

4.1. White Matter Microstructural Change in Both Hemispheres

As mentioned in the results section, significant differences between the Cingulum, AF, SLF, IFOF, and ILF of both hemispheres in PPA patients and HC individuals were noticed. Similar variances have been reported in prior studies [10, 25, 44, 45]. Furthermore, UF differential changes in the left hemisphere were observed. Over the last decade, increasing evidence has supported a dual-stream model of language. This model proposes that two distinct pathways, both anatomically and functionally, work together to facilitate language learning and processing [46, 47].

The left-dominant dorsal pathway primarily comprises the SLF and AF, while the more bilaterally organized ventral pathway is inclusive of the IFOF, UF, ILF, and middle longitudinal fasciculus [48-51]. The dorsal stream is believed to support phonological processing and motor-articulatory computations [47, 48], while the ventral stream is linked to lexical-semantic processing [48]. Consequently, it is anticipated that impairments exist in the pathways of this group of patients.

Studies have shown that in patients with PPA, white matter atrophy, including in the cingulum, is associated with language impairments [52]. Additionally, the cingulum has been linked to variations in Alzheimer's pathology in individuals with aphasic dementia, highlighting its role in language-related cognitive decline [53]. Abnormal fiber metrics have been found in the cingulum of individuals with mild cognitive impairment. These individuals encounter difficulties with memory, language, and visuospatial functions [54].

In the present study, CC and fornix impairments in the PPA group have been observed. The impairment of the relevant tracts has been previously reported for this group of patients [10, 52]. The CC, as the largest fiber tract in the brain, plays a crucial role in integrating motor and sensory information between the two cerebral hemispheres. This integration is essential for various cognitive functions, including executive function, social interaction, and language processing [55, 56]. Moreover, the fornix has been linked to language function, as part of a network that includes the hippocampus and parahippocampal cortex, crucial for declarative memory and encoding and retrieval processes [57]. In very preterm infants, the organization of verbal information has been associated with the cingulum and fornix volume, indicating a relationship between these tracts and language development [58].

4.2. White Matter Microstructural Change and Language Processing in Both Hemispheres

The present study observed positive and negative correlations between the left Cingulum diffusivity values and various language functions such as fluency, writing, repetition, and comprehension. Studies have shown that the cingulum is involved in language-related tasks such as phonological processing, language switching, picture naming, and verbal memory [59-61]. Additionally, the cingulum has been associated with cognitive domains like attention, executive functions, and memory, which are essential for language production and comprehension [61, 62].

The left SLF showed negative correlations with aphasia quotient, single-word comprehension, oral reading, and auditory comprehension. Considering the SLF as part of the dorsal pathway, it can be assumed it participates in complex syntactic processes [27, 63]. Previous studies suggest that aside from its traditional role in speech repetition from sound to articulation, the SLF also plays a syntactic role, as indicated by lesion mapping and functional MRI studies [39, 64].

The left ILF, as part of the ventral language system, exhibited negative and positive correlations with single-word and auditory comprehension. The integrity of the left ILF is linked to single-word comprehension performance [19, 40]. The meta-analysis by Zhang *et al.*, (2021) supported the correlation between ILF and comprehension [65].

In the present study, the FA of right IFOF, ILF, and SLF showed a positive correlation with different language domains, including aphasia quotient, PNT, single-word and auditory comprehension, and repetition. A study has found that the right IFOF is involved in non-verbal semantic memory (non-verbal). Other studies have suggested that the right IFOF and right ILF may play a role in naming recovery in post-stroke aphasia [48]. Furthermore, these tracts as part of the ventral language pathway are crucial for the intra-hemispheric transfer of information between frontal and posterior cortices, contributing to language semantics and comprehension [66, 67]. Moreover, Chen *et al.* (2020) found a negative correlation between the right SLF and ILF with memory function [68]. Considering the progressive nature of PPA, it can be assumed that the observed correlation between right SLF and behavioral language symptoms is due to the possible maladaptive role of RH in language performance [12]. Therefore, longitudinal studies are necessary to assess RH microstructural changes at baseline and in subsequent years in this group of patients.

The compensatory or maladaptive role of RH in language processing is not clear and controversial evidence reported in previous literature [69, 70]. However, stimulation of the RH seems to enhance language function, regardless of its role in language processing [71].

4.3. White Matter Microstructural Change and Neuropsychological Functions in both Hemispheres

The left Cingulum and CC had positive and negative correlations with MMSE and P-DAD scores, respectively. As mentioned earlier, the Cingulum is associated with cognitive domains like attention, executive functions, and memory [61, 62]. In the context of stroke studies, lesions to the corpus callosum have been associated with upper extremity motor function deficit, which can lead to general disability and impact activities of daily living [72, 73]. Furthermore, the callosal projection of CC to the prefrontal cortex the cingulate cortex involved in executive attention network functions [72].

The current study indicated a positive correlation between the right IFOF and P-DAD, as well as P-FAB while showing a negative correlation with CDT and P-NPI. The right IFOF is a long-range association fiber that connects various brain regions involved in cognitive functions such as attention, inhibition, and visual processing [74, 75]. Moreover, the IFOF has been associated with activities of daily living, contributing to executive function, and goal-oriented behavior [76]. Additionally, Disruptions in the IFOF have been observed in various neuropsychiatric disorders, such as schizophrenia, generalized anxiety, obsessive-compulsive disorder, and depression [77-79]. Overall different neural pathways serve specific functions, and evaluating these functions reveals a stronger correlation among certain pathways compared to others. Designing cognitive rehabilitation programs that engage both hemispheres of the brain may enhance the cognitive and behavioral symptoms experienced by patients with PPA.

To the best of our knowledge, this is the first study to identify a specific correlation between RH tracts, language domains, and cognitive functions in patients with PPA. Neophytou *et al.* (2023) demonstrated the right hemisphere's role in language processing, but any specific statistically significant relationships between language and individual right hemisphere tracts were not established [12].

4.4. Study Limitations

While the present study provides valuable insights, it is important to acknowledge its limitations. The cross-sectional nature of the research prevents the authors from concluding the progression of white matter changes over time. Future longitudinal studies are necessary to assess the evolution of microstructural changes, particularly in the right hemisphere, and their relationship with language and cognitive decline in PPA. Such studies could provide crucial information about the trajectory of the disease and potentially identify early markers of PPA progression. Moreover, the research encountered limitations within the PPA group, which consisted of differing and unequal numbers of participants for each subtype. It is conceivable that the findings documented in this study may not be uniform across the three PPA subtypes. Hence, forthcoming studies should investigate whether and how the findings specified in this study differ across PPA subtypes. Furthermore, longitudinal tracking of WM changes in PPA subtypes can improve the diagnostic evaluation of these groups of patients.

5. Conclusion

The present study examined microstructural changes in white matter tracts in patients with PPA and their impact on language and cognitive functions. Our findings revealed significant alterations in diffusivity values of several WM tracts, including the Cingulum, AF, SLF, IFOF, and ILF in both hemispheres, indicating extensive WM degradation in PPA. The results supported the dual-stream model of language processing, showing involvement from both the dorsal and ventral pathways, correlating with impairments in phonological processing, motor functions, and lexical-semantic abilities.

Beyond language, significant correlations were found between WM integrity and neuropsychological functions, including measures of executive function linked to the right IFOF. The widespread impairments

in the CC indicated disruptions in inter-hemispheric communication and memory processes.

To our knowledge, this study is the first to highlight the role of RH tracts in language and cognitive functions in PPA. This finding challenges the traditional view of language processing being predominantly left-hemisphere-focused and suggests a more significant role for the right hemisphere in neurodegenerative conditions. Rehabilitation programs targeting linguistic and cognitive functions and neuromodulation strategies focusing on the RH may improve language, cognitive, and behavioral symptoms.

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