Correlations between Dual-Pathway White Matter Alterations and Language Impairment in Patients with Aphasia

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REVIEW

Correlations between Dual-Pathway White Matter Alterations and Language Impairment in Patients with Aphasia: A Systematic Review and Meta-analysis

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Abstract

While converging evidence suggests linguistic roles of white matter tracts, detailed associations between white matter alterations of dual pathways and language abilities remain unknown in aphasic patients. We aimed to verify language functions of dual-pathway tracts from specific domains and investigate the influence of moderators. PubMed, Web of Science, Embase, and CENTRAL were searched for studies published between January 1, 1985 and March 17, 2019. A meta-analysis of 46 studies including 1353 aphasic patients was performed by pooling correlation coefficients between linguistic domains and diffusion metrics of dual-pathway tracts. Among these tracts, the fractional anisotropy (FA) value of the left inferior fronto-occipital fasciculus predominated across most linguistic aspects, showing the strongest correlations with global severity, comprehension, naming and reading ability. The left uncinate fasciculus and inferior longitudinal fasciculus also showed significant FA – comprehension correlations. For syntactic processing, FA values of the left superior longitudinal fasciculus and arcuate fasciculus showed significant positive correlations. Meta-regression revealed no influence of etiology on FA – language correlations, while sex had a moderating effect on the FA – comprehension correlation of the arcuate fasciculus, and age influenced the FA – naming correlation in the superior longitudinal fasciculus. In conclusion, multifunctional characteristics of tracts were revealed in aphasic patients, including broad linguistic associations of the inferior fronto-occipital fasciculus, and repetition and syntactic involvement of the arcuate fasciculus. Language associations of the inferior longitudinal fasciculus and uncinate fasciculus were clarified regarding comprehension subdomains. The insignificant moderating effect of the etiology indicates damage of dual pathways is the common neural mechanism, while sex and age influence the correlation with comprehension and naming ability, respectively, in specific tracts.

Keywords Aphasia · Diffusion tensor imaging · White matter · Dual pathway

Introduction

Aphasia is a common symptom after brain damage. Various cerebral diseases, including stroke, tumor, traumatic brain injury (TBI), neurodegenerative diseases, and epilepsy, can lead to language impairment. Because language is a special ability that differentiates humans from other species, the mechanisms and prognosis of language deficits have long been of interest to neuroscientists (Patel, 2003). Recently, the classic language model based on perisylvian

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cortical regions has been challenged by neuroimaging and stimulation mapping studies (Chang et al., 2015; Tremblay & Dick, 2016). Apart from cortical regions, damage to subcortical white matter tracts can also contribute to aphasia (Dronkers et al., 2007; Sathian & Crosson, 2015).

With the advent of diffusion tensor imaging (DTI), diffusion metrics, including fractional anisotropy (FA), are used to reflect microstructural damage to white matter such as demyelination and axonal damage (Basser & Jones 2002). Advanced diffusion models use fixel-based measures, such as fiber density and fiber cross-section, which show better interpretability for crossing fiber bundles (Raffelt et al., 2017). Other diffusion techniques with precise microstructural mapping include neurite orientation dispersion and density imaging, composite hindered and restricted model of diffusion, and diffusional kurtosis imaging (Assaf & Basser 2005; Jensen et al., 2005; Zhang et al., 2012).

Contemporary language models propose that extensive white matter tracts are involved in language processing (Dick et al., 2014; Friederici, 2012; Friederici & Gierhan, 2013). Several major tracts constitute the prevailing dual-pathway language model: a dorsal pathway supporting sound-to-articulation mapping and a ventral pathway subserving sound-to-meaning mapping (Friederici, 2012; Hickok & Poeppel, 2007; Saur et al., 2008; Fig. 1). The dorsal pathway mainly consists of the ventral superior longitudinal fasciculus and arcuate fasciculus. The superior longitudinal fasciculus has three main branches (Thiebaut de Schotten et al., 2011), of which only the ventral component, called superior longitudinal fasciculus III, is involved in language processing. The superior longitudinal fasciculus III connects the supramarginal gyrus with ventral premotor and prefrontal regions (Makris et al., 2005). The arcuate fasciculus is a left-lateralized tract, extending from the inferior frontal lobe, and terminates in the posterior superior temporal gyrus and the middle temporal gyrus (Catani et al., 2005; Glasser & Rilling, 2008). A novel frontal pathway associated with speech initiation and verbal fluency, the frontal aslant tract connects the pars opercularis of the inferior frontal gyrus with the supplementary motor area (SMA) and presupplementary motor area (pre-SMA) (Catani et al., 2012). In parallel, the ventral pathway is composed of the inferior fronto-occipital fasciculus, uncinate fasciculus, inferior longitudinal fasciculus, and middle longitudinal fasciculus (Catani et al., 2002; Forkel et al., 2014b; Makris et al., 2009; Menjot de Champfleur et al., 2013). The inferior fronto-occipital fasciculus is an anterior–posterior tract connecting the frontal lobe to the temporobasal areas, superior parietal lobe, and occipital cortex (Catani et al., 2002; Martino et al., 2010). While the uncinate fasciculus is a more medio-ventral tract joining the medial and lateral orbitofrontal cortex with anterior temporal lobe (Catani et al., 2002), the inferior longitudinal fasciculus connects the anterior temporal region to posterior occipitotemporal regions (Catani et al., 2003). In addition, recent research has delineated the middle longitudinal fasciculus in human brains, which links the inferior parietal lobule with the superior temporal gyrus (Makris et al., 2009).

Recently, a large volume of DTI studies of aphasic patients has indicated that damaged fiber tracts of the dual

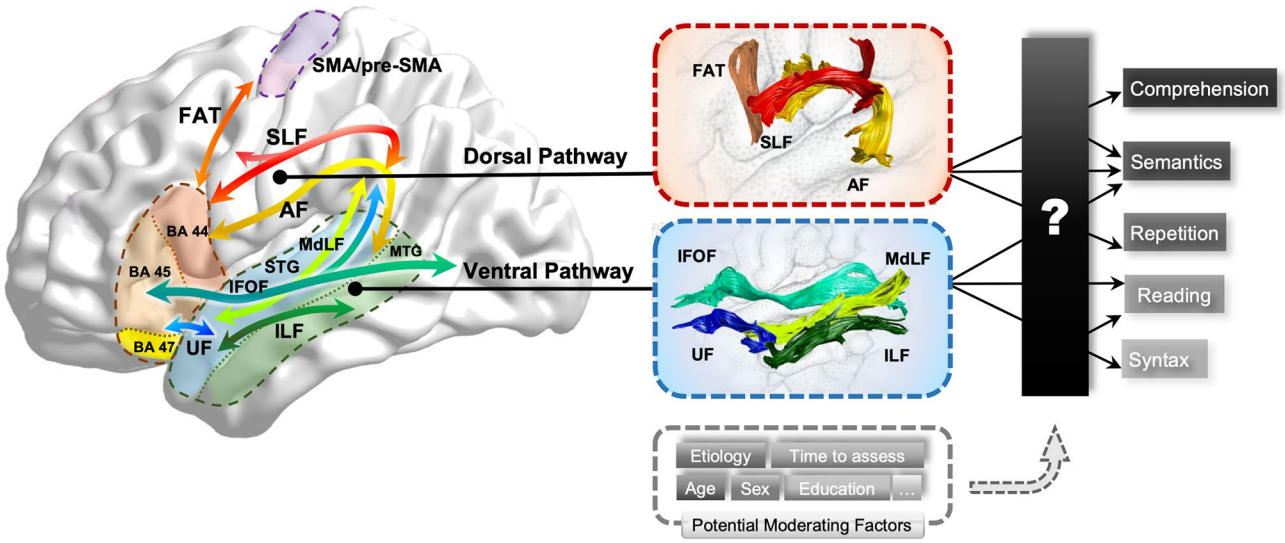


Fig. 1 Dorsal and ventral fiber tracts in the dual-pathway language model, potential moderating factors, and their complicated associations with multiple linguistic aspects. *Note:* SLF, superior longitudinal fasciculus; AF, arcuate fasciculus; FAT, frontal aslant tract; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus; ILF, inferior longitudinal fasciculus; MdLF, middle longitudinal fasciculus; BA, Brodmann Area; STG, superior temporal gyrus; MTG, middle temporal gyrus; SMA, supplementary motor area

pathways are associated with language impairment. These studies have several remarkable advantages. First, although most individual DTI studies merely focused on one or only a few tracts, these studies together examine a broad range of language-related tracts. These findings covered the tracts in the dual-pathway model, and subtest scores of various language domains were investigated. Second, the etiology of aphasia was not limited in these studies, and included stroke, brain tumor resection (Griffiths et al., 2013; Sierpowska et al., 2020), TBI (Elbourn et al., 2019; Han et al., 2016), primary progressive aphasia (PPA) (Agosta et al., 2010; Catani et al., 2013; Forkel et al., 2020; Ulugut Erkoyun et al., 2020), electronic shock, and gas poisoning (Han et al., 2013). These results provide tract-linguistic correlates to find the common critical mechanism of language deficits that underlie different pathophysiological causes.

In spite of the above strengths, these individual studies have some limitations. First, there are still inconsistencies regarding the linguistic role of specific tracts. The language function of the uncinate fasciculus is still debated (Papagno et al., 2011). The FA value of the left uncinate fasciculus showed a significant positive correlation with comprehension in some studies (Catani et al., 2013; Zaizhu Han et al., 2013), while another showed no significant correlation (Ivanova et al., 2016). There are also inconsistent conclusions about the overall indicative role of a tract among different DTI studies (Forkel et al., 2014a; Jang et al., 2017; Kim & Jang, 2013; Rosso et al., 2015). Secondly, it is in dispute whether a complicated fasciculus is associated with linguistic roles in addition to the widely-accepted traditional function (Sarubbo et al., 2013; Wu et al., 2016). Lastly, it remains unknown whether moderators such as age, sex, education, time to assessment, and etiology of aphasia have an influence on the relationship between language performance and white matter integrity. Overall, a meta-analysis is needed to reduce the uncertainty and inconsistency of current individual studies.

In this context, the primary purpose of this meta-analysis was to corroborate the linguistic associations of dual-pathway tracts and to investigate the influence of potential moderators. The between-group differences of diffusion metrics were also investigated to identify the underlying microstructural alterations. We hypothesized that dual-pathway tracts have multiple associations with different language domains and can illustrate the common neural fundamentals for aphasia.

Methods

Search Strategy and Selection Criteria

This systematic review and meta-analysis was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

We searched studies published between January 1st 1985 and March 17th 2019 in PubMed, Embase, Web of Science (WOS) and the Cochrane Central Register of Controlled Trials (CENTRAL). These databases were retrieved to select relevant studies with the following Medical Subject Heading (MeSH) terms, keywords and their synonyms: "aphasia", "pathway*" and "diffusion tensor imaging" (see the Supplementary material for the complete search strategy). Furthermore, we manually checked the references of recent reviews for additional studies, and searched for ongoing studies from other sources such as Clinicaltrials.gov.

We considered studies for inclusion if (1) patients were diagnosed with aphasia, and the first language of patients was not limited, (2) language performance was evaluated by standard scales, (3) DTI scanning was performed to measure white matter integrity of dual-pathway tracts, and (4) the results were suitable for effect size calculation, such as between-group diffusion metrics, or correlation coefficients between diffusion metrics and linguistic scores. In addition, studies were excluded if (1) patients had been confirmed with cognitive, emotional or psychiatric disorders, (2) patients had dysarthria, (3) participants had a history of alcohol or other drug use, or use of psychoactive medications, (4) all cases were pediatric patients, and (5) the studies were regarded as overlapping with a prior published study.

This study was registered at International Prospective Register of Systematic Reviews (PROSPERO), number CRD42018089597.

Data Extraction and Quality Assessment

Study eligibility was checked by two investigators (J.Z. and S.Z.), and relevant data were extracted independently by Y.M.Y. and M.W. Characteristics of included studies and relevant quantitative results were tabulated in a spreadsheet. Discussions with or referrals to senior investigators (L.Z. and X.F.T.) were arranged when disagreements arose between two investigators.

Two independent reviewers (Y.M.Y. and M.W.) assessed the quality of the selected studies using a scale named the Quality Assessment of Diagnostic Studies 2 (QUADAS-2). The figures for the quality assessment were made using RevMan 5.3 (Review Manager 5.3, Cochrane Informatics and Knowledge Management Department).

Outcomes

Given the difficulty of obtaining original imaging data from individual studies, we merged accessible data that were reported in the results of published studies, namely, mean

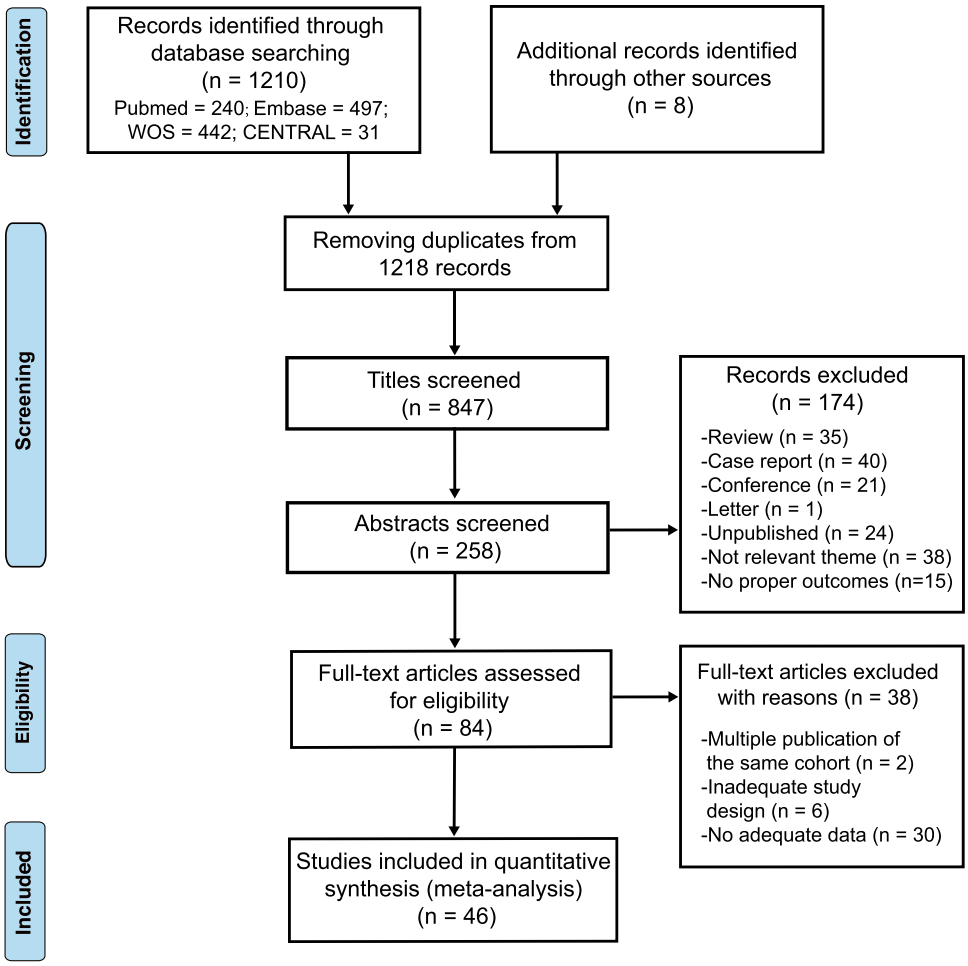


Fig. 2 Flow chart of the screening and selection of studies. *Note:* WOS, Web of Science, CENTRAL, Cochrane Central Register of Controlled Trials

values of diffusion metrics and correlation coefficients. Compared with other indices, the FA value is a robust index that is not significantly affected by diffusion sensitization parameters, including the number and strength of b values (Li et al., 2004; Melhem et al., 2000; Zhang et al., 2004). Our primary measure of the effect size was the correlation coefficient between linguistic scores and FA in aphasic patients. All of the trials included in our study had performed region of interest (ROI) analysis, and the FA was extracted from tracts of interest, namely, major tracts in the dorsal and ventral pathways. Some of the included trials used both ROI and whole-brain level analyses. Fom such studies, we only extracted the data from the results of the ROI analysis.

Linguistic abilities were assessed by standard scales, including the Boston Naming Test (BNT; Kaplan, 1983), Aphasia Battery of Chinese (ABC; Gao, 2006), and different language versions of the Western Aphasia Battery (WAB; Kertesz, 2007). The global severity of aphasia was measured by the aphasia quotient (AQ) of the WAB or Aphasia Rapid Test (ART; Azuar et al., 2013). The AQ was calculated by a specific formula, with higher scores indicating better performance: AQ = (Spontaneous fluency score/20 + Comprehension score/20 + Repetition score/20 + Naming score/10) *2. Specific scores covered the following aspects of language processing: repetition, comprehension, naming, reading, and syntax. Definitions and subtests of aforementioned language domains are tabulated in Table S1. Correlation coefficients were merged for analysis only if the tests measured the same language domain. Detailed subdomains were also investigated separately if data were available. For instance, comprehension is a wide concept with complicated processing, so we investigated several subdomains of comprehension from levels of single word comprehension, sentence comprehension, and semantic association.

Secondary outcomes, that were investigated included relationships between language performance and other diffusion metrics such as mean diffusivity, axial diffusivity, and radial diffusivity. In addition, we collected the mean values of diffusion metrics from studies, where available. Comparisons between patient and control groups were conducted to investigate the overall differences.

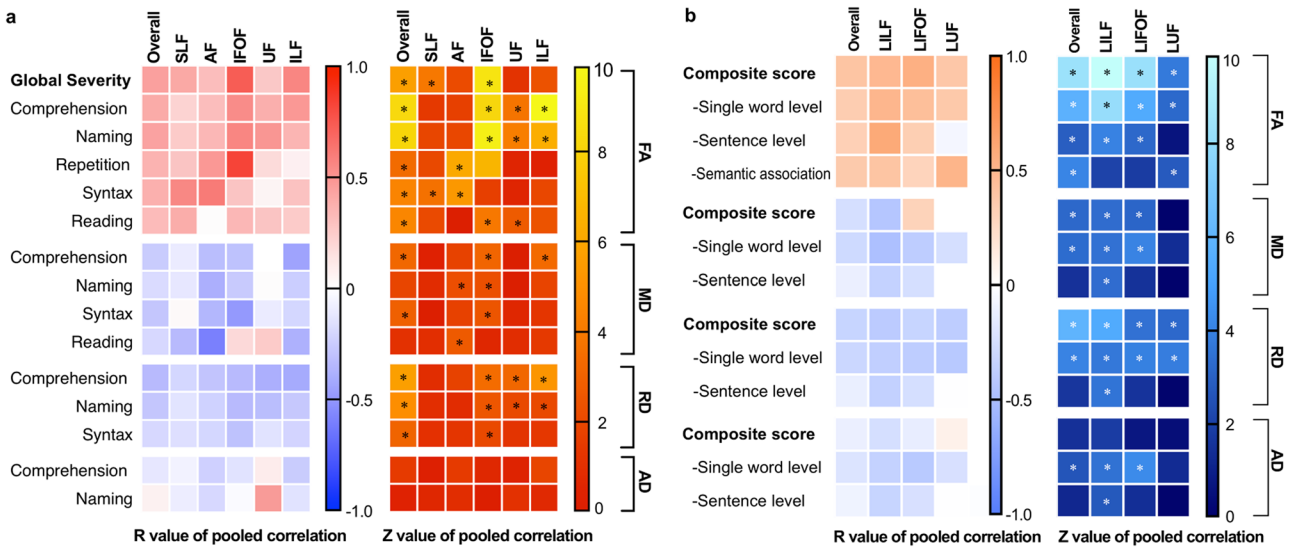


Fig. 3 Correlation matrices rendered by color scales. **a** correlations between language domains and diffusion metrics of the left dorsal and ventral tracts; **b** correlations between subdomains of comprehension and the left ventral tracts. *Note:* R values represent magnitude of pooled correlations, and Z values of meta-analytic tests indicate the statistical power of significance ($P < 0.05$ by Bonferroni's correction, marked with asterisks). Gray squares denote those correlations that did not report in the merged data. CI, confidence interval; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; SLF, superior longitudinal fasciculus; AF, arcuate fasciculus; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus; ILF, inferior longitudinal fasciculus

Statistical Analysis

For the primary outcome of correlation coefficients, Fisher transformation was performed to convert Pearson correlation coefficients into a Fisher's z value by the following formula: $r_{Spearman} = \frac{6}{\pi} \sin^{-1} \frac{r_{Pearson}}{2}$. As Fisher's z values followed the normal distribution, their variability could be estimated by the standard error (SE) and 95% confidence intervals (CIs). For the second outcome of mean diffusion metrics, we used a standardized mean difference (SMD) to estimate the effect size and standard deviation (SD) to estimate the variability.

All statistical analyses were performed in StataSE 13 (Stata-Corp, College Station, TX, USA). We chose a random-effects model (inverse variance method) for the meta-analyses. Overall correlation coefficients, pooled estimates of mean differences, and their 95% CIs were calculated. Q-statistics and the I^2 index were used to evaluate the heterogeneity among studies and $I^2 > 50\%$ was regarded as substantial heterogeneity. The significant threshold was adjusted for multiple correlations (k) by Bonferroni's correction ($p < 0.05/k$). In the meta-analyses of each linguistic aspect, subgroups were assigned according to white matter tracts or diffusion metrics. Meta-regression analyses were performed to detect potential moderators for correlations with enough studies. In addition, we used funnel plots and Egger's test to detect the publication bias for results with enough studies, setting p value < 0.1 as statistically significant.

Results

Study Selection and Characteristics

We identified 1218 records, of which 306 records were duplicates (Fig. 2). After the initial screening, abstracts of the 371 studies whose titles fitted the inclusion criteria were assessed further for the eligibility. Finally, 84 studies were selected for full-text assessment, of which 46 eligible studies remained. Of the 46 studies selected for quantitative synthesis, 33 studies investigated the correlations between language scores and imaging metrics, and 23 reported differences of diffusion metrics between patients and controls.

All 46 included studies were published between 2007 and 2019 (Table S2). The current systematic review and meta-analysis comprises of 1353 patients, of which 65% were male patients. The mean age of the patient group ranges from 20.1 to 69.6 years. Mean disease duration varies between 2 days to 7.5 years, and most of the included studies had enrolled chronic aphasic patients. The first languages of assessment included English, German, French, Dutch, Russian, Korean, and Chinese. Stroke was the most predominant etiology of aphasia in 30 studies, followed by PPA in 11 studies. Other causes such as brain tumor and TBI were also included. The prevailing analytic method was ROI-based fiber tractography, focusing on regions of the

superior longitudinal fasciculus, arcuate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, middle longitudinal fasciculus, and frontal aslant tract. Regarding scanning characteristics, the MRI protocols are listed in Online Resource 2 (Table S3).

Quality Assessment of Studies

The methodological quality of the studies is shown in the risk of bias graph and risk of bias summary (Online Resource 3, Fig. S1 – 2). The original judgments are listed in Online Resource 2 (Table S4). In the domain of patient selection, 32.6% of studies were considered high risk due to inappropriate inclusions or exclusions and 56.5% were an unclear risk with insufficient details regarding consecutive or random enrollment procedure. We also detected a moderate risk of bias for flow and timing (Unclear risk: 41.3%; Low risk: 26.1%; High risk: 32.6%). By contrast, the risk of bias introduced by the index test and reference standard was much lower. As a whole, there were considerable risks of bias in these DTI studies, but the overall clinical applicability was acceptable.

Pooled Group-wise Diffusion Metric Differences

As shown in Fig. S3 (Online Resource 3), we found that the overall between-group differences of the four diffusion metrics in the left tracts were all significant (all $p < 0.01$). For instance, aphasic patients showed lower FA values than the healthy participants (SMD -1.37, 95% CI [-1.59, -1.16]), whereas mean diffusitivity (SMD 1.21, 95% CI [0.95, 1.46]), axial diffusitivity (SMD 0.75, 95% CI [0.43, 1.07]), and radial diffusitivity (SMD 1.05, 95% CI [0.87, 1.23]) were significantly higher compared to controls. The heterogeneity of the overall results was significant (all $I^2 > 50\%$; $p < 0.01$). Subgroup analyses predefined by tracts of interest (the left superior longitudinal fasciculus, uncinate fasciculus, and inferior longitudinal fasciculus) showed reduced heterogeneity (Fig. S3; all $p > 0.05$).

Meta-analyses of Language – Imaging Correlations

The correlation between language domains and imaging metrics was the primary outcome of this study (Fig. 3a). Detailed role of ventral tracts for comprehension subdomains is shown in Fig. 3b. The number of studies and number of patients for pooled correlations between different domains and fiber tracts are summarized in Table 1. The number of studies reporting correlations with the left frontal aslant tract and middle longitudinal fasciculus was not enough for meta-analysis. Correlations with dorsal and ventral pathways were categorized by language domains as described in the following sections.

Global Severity of Aphasia

As shown in Fig. 4, the pooled correlation between the AQ and FA for left tracts, overall, was significant ($r = 0.44$, $p < 0.001$, 95% CI [0.29, 0.58]), but the heterogeneity was substantial ($I^2 = 74.7\%$, $p < 0.001$). Subgroup analyses of tracts of interest revealed that the left inferior fronto-occipital fasciculus showed the strongest correlation ($r = 0.73$, $p < 0.001$, 95% CI [0.57, 0.89]) with smaller heterogeneity ($I^2 = 34.0\%$, $p = 0.208$). In the dorsal pathway, the left superior longitudinal fasciculus showed smaller but significant correlations with AQ (superior longitudinal fasciculus: $r = 0.41$, 95% CI [0.20, 0.62]; $p < 0.001$).

Regarding mean diffusitivity and radial diffusitivity, none of the tracts showed significant pooled correlations with global severity (all corrected $p > 0.05$).

Comprehension and Subdomains

As shown in Fig. 5 and Fig. S4 (Online Resource 3), the FA of the left tracts significantly correlated with comprehension ability ($r = 0.40$, $p < 0.001$, 95% CI [0.31, 0.49]). Across different tracts of interest, the left inferior fronto-occipital fasciculus showed the strongest FA – comprehension correlation ($r = 0.53$, $p < 0.001$, 95% CI [0.40, 0.66]) with low heterogeneity ($I^2 = 36.8\%$, $p > 0.05$). The left inferior longitudinal fasciculus ($r = 0.48$, $p < 0.001$) and uncinate fasciculus ($r = 0.38$, $p < 0.001$) also showed significant positive correlations. However, the FA values of the left dorsal tracts (superior longitudinal fasciculus and arcuate fasciculus) did not correlate with comprehension significantly (both corrected $p > 0.05$). Additionally, negative weak correlations were detected between comprehension and the other three diffusion metrics (Fig. 3a).

Subgroup analyses of comprehension subdomains (Fig. 5 and Online Resource 3, Fig. S5) showed significant correlations between sentence-level comprehension and FA of the left inferior longitudinal fasciculus ($r = 0.39$, $p < 0.001$) and inferior fronto-occipital fasciculus ($r = 0.33$, $p = 0.002$), while semantic association correlated significantly with uncinate fasciculus ($r = 0.51$, $p = 0.006$). Regarding single-word level, the FA values of all three ventral tracts showed significant correlations (inferior longitudinal fasciculus: $r = 0.48$; inferior fronto-occipital fasciculus: $r = 0.53$; uncinate fasciculus: $r = 0.38$; all corrected $p < 0.05$).

Naming

In the domain of naming, only the correlations with left ventral tracts were significant (Fig. 6 and Online Resource 3, Fig. S6). The FA of the left inferior fronto-occipital

Table 1 Number summary of studies and patients from meta-analyses for correlation between each domain and fiber tract

Diffusion Index	Language Domain	Left SLF (N/n)	Left AF (N/n)	Left IFOF (N/n)	Left UF (N/n)	Left ILF (N/n)	Left FAT (N/n)	Overall (N/n)
FA								
	Global severity	3/66	7/136	4/70	3/64	1/11	2/53	10/226
	Comprehension							
	-Composie score	7/233	6/154	7/237	7/227	9/274	2/60	13/395
	-Single word level	3/96	3/91	4/105	5/140	6/162	2/60	9/238
	-Sentence level	2/77	3/102	2/77	2/77	2/77	NA	3/102
	-Semantic association	1/76	NA	3/131	2/86	1/25	NA	4/156
	Naming	5/220	5/137	7/273	8/308	6/256	NA	9/335
	Repetition	2/43	4/101	1/11	2/46	2/43	2/53	7/186
	Syntax	3/89	3/76	3/78	3/99	1/37	NA	5/138
	Reading	4/98	2/31	4/108	2/80	2/80	NA	5/118
MD								
	Global severity	2/48	2/36	NA	NA	NA	NA	3/73
	Comprehension							
	-Composie score	2/48	4/102	3/88	3/88	4/93	NA	5/107
	-Single word level	NA	3/91	2/77	2/77	3/82	NA	4/96
	-Sentence level	NA	2/77	2/77	2/77	2/77	NA	2/77
	Naming	2/48	3/65	3/65	3/65	2/48	NA	3/65
	Repetition	NA	NA	NA	1/35	NA	NA	1/35
	Syntax	NA	2/51	2/51	NA	NA	NA	2/51
	Reading	3/26	NA	2/19	NA	NA	NA	4/34
RD								
	Global severity	2/48	NA	NA	2/46	NA	NA	3/83
	Comprehension							
	-Composie score	3/73	4/102	3/88	5/148	4/113	NA	6/162
	-Single word level	NA	3/91	2/77	4/137	2/77	NA	5/151
	-Sentence level	NA	2/77	2/77	2/77	2/77	NA	2/77
	Naming	2/48	2/48	2/48	3/83	2/48	NA	3/83
	Syntax	2/62	NA	NA	2/72	NA	NA	3/97
AD								
	Comprehension							
	-Composie score	2/48	4/102	3/88	3/88	3/88	NA	4/102
	-Single word level	NA	3/91	2/77	2/77	2/77	NA	3/91
	-Sentence level	NA	2/77	2/77	2/77	2/77	NA	3/91
	Naming	2/48	2/48	2/48	2/48	2/48	NA	2/48

N, number of studies; *n*, number of patients; *NA*, not applicable

fasciculus showed the strongest correlation (r = 0.56, $p < 0.001$, 95% CI [0.44, 0.68]), followed by the left uncinate fasciculus ($r = 0.49$, $p < 0.001$, 95% CI [0.26, 0.72]) and inferior longitudinal fasciculus ($r = 0.35$, $p < 0.001$, 95% CI [0.24, 0.46]). Subgroup analyses by tracts of interest showed that the heterogeneity of left inferior longitudinal fasciculus and inferior fronto-occipital fasciculus were low.

Regarding the other metrics, radial diffusitivity and mean diffusitivity presented negative correlations with naming, whereas there were no significant findings for axial diffusitivity (Fig. 3a).

Repetition

The overall FA – repetition correlation was moderately positive and significant (see Online Resource 3, Fig. S7; $r = 0.36$, $p = 0.001$, 95% CI [0.15, 0.58]), and the heterogeneity was substantial ($I^2 = 75.7\%$, $p < 0.001$).

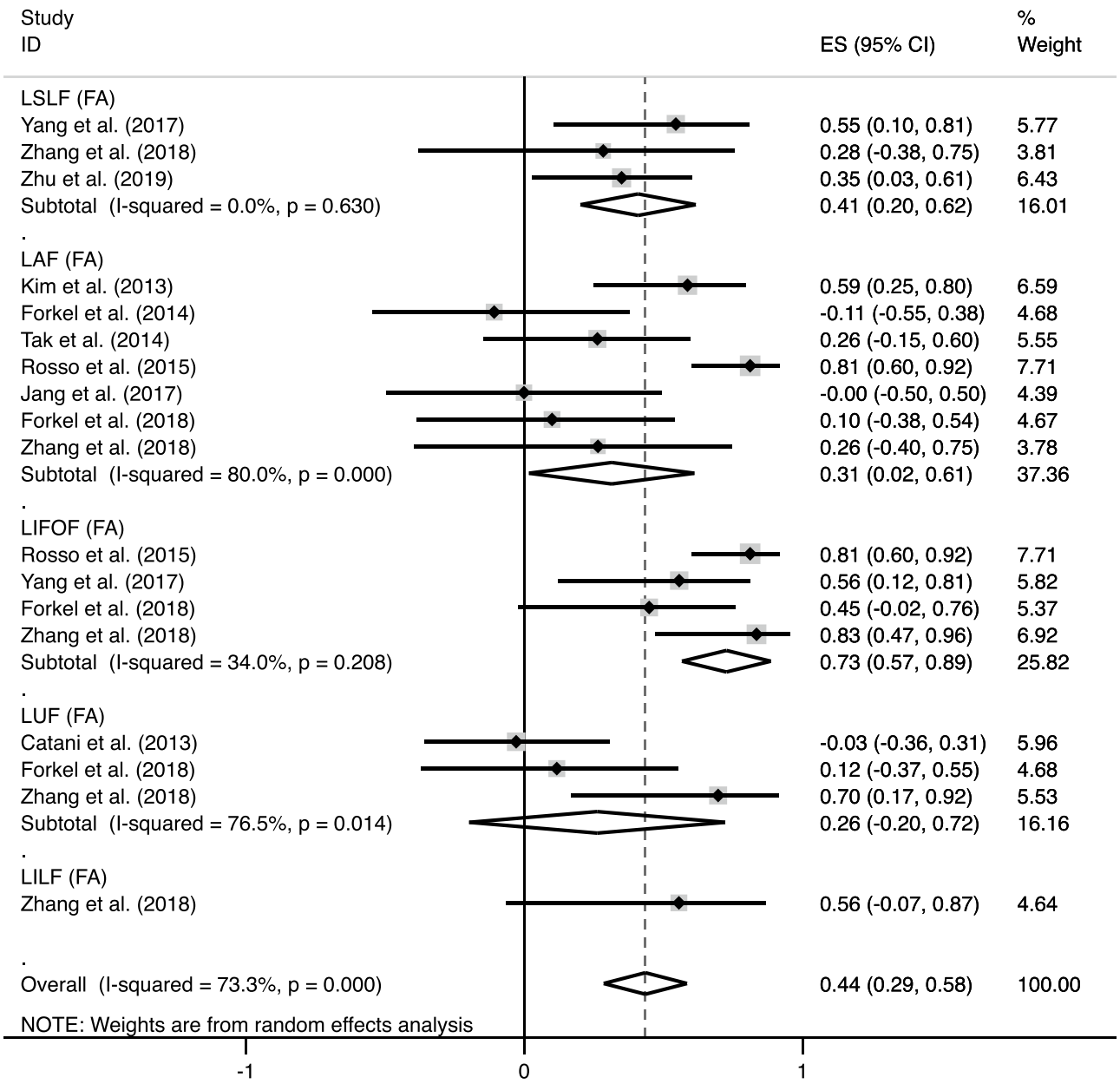


Fig. 4 Forest plot of correlations between FA and global severity of aphasia in the left dorsal and ventral tracts. *Note:* Diamonds represent overall or subtotal r values of correlation coefficients. FA, fractional anisotropy; CI, confidence interval; LSLF, left superior longitudinal fasciculus; LAF, left arcuate fasciculus; LIFOF, left inferior fronto-occipital fasciculus; LUF, left uncinate fasciculus; LILF, left inferior longitudinal fasciculus

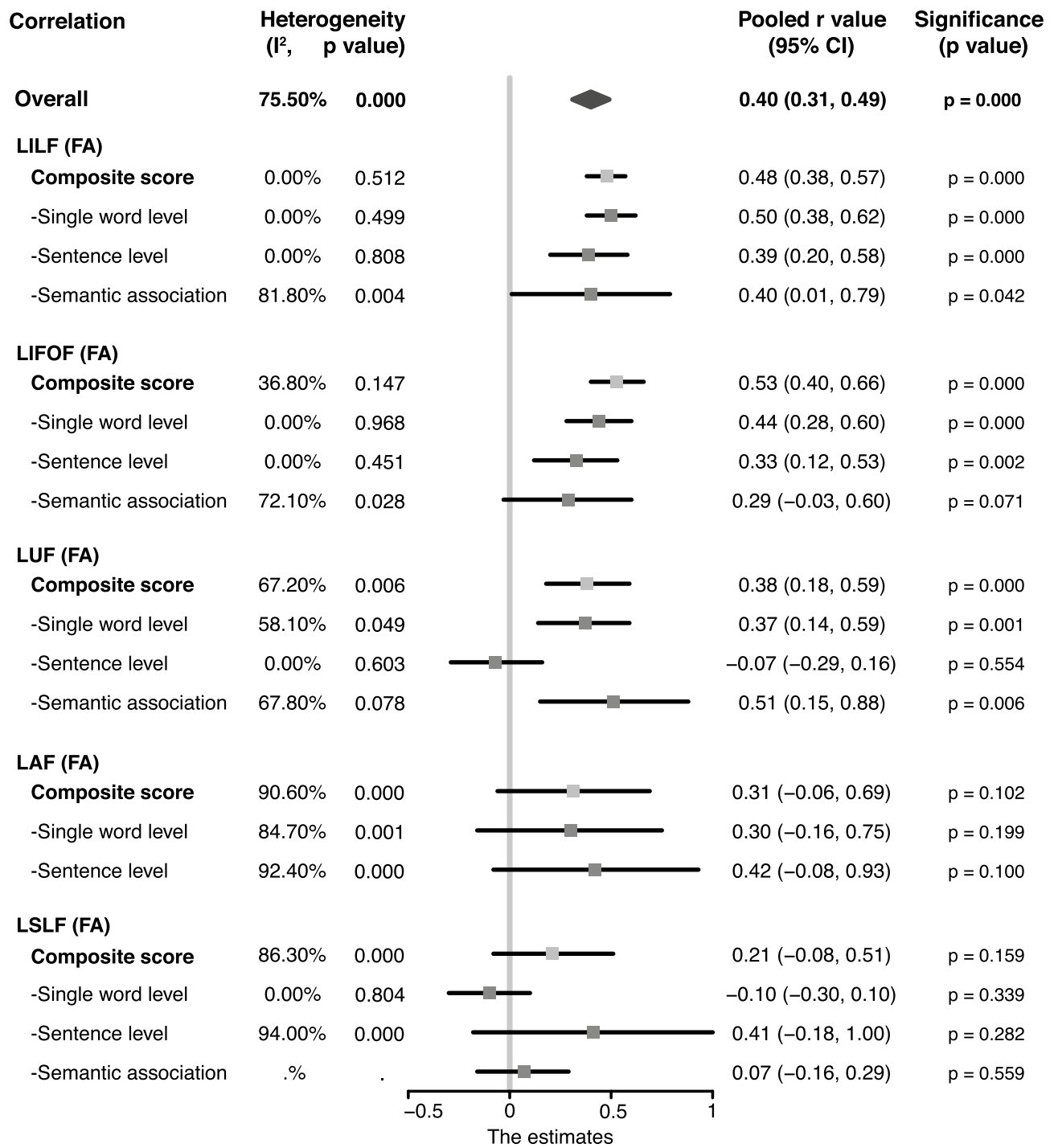
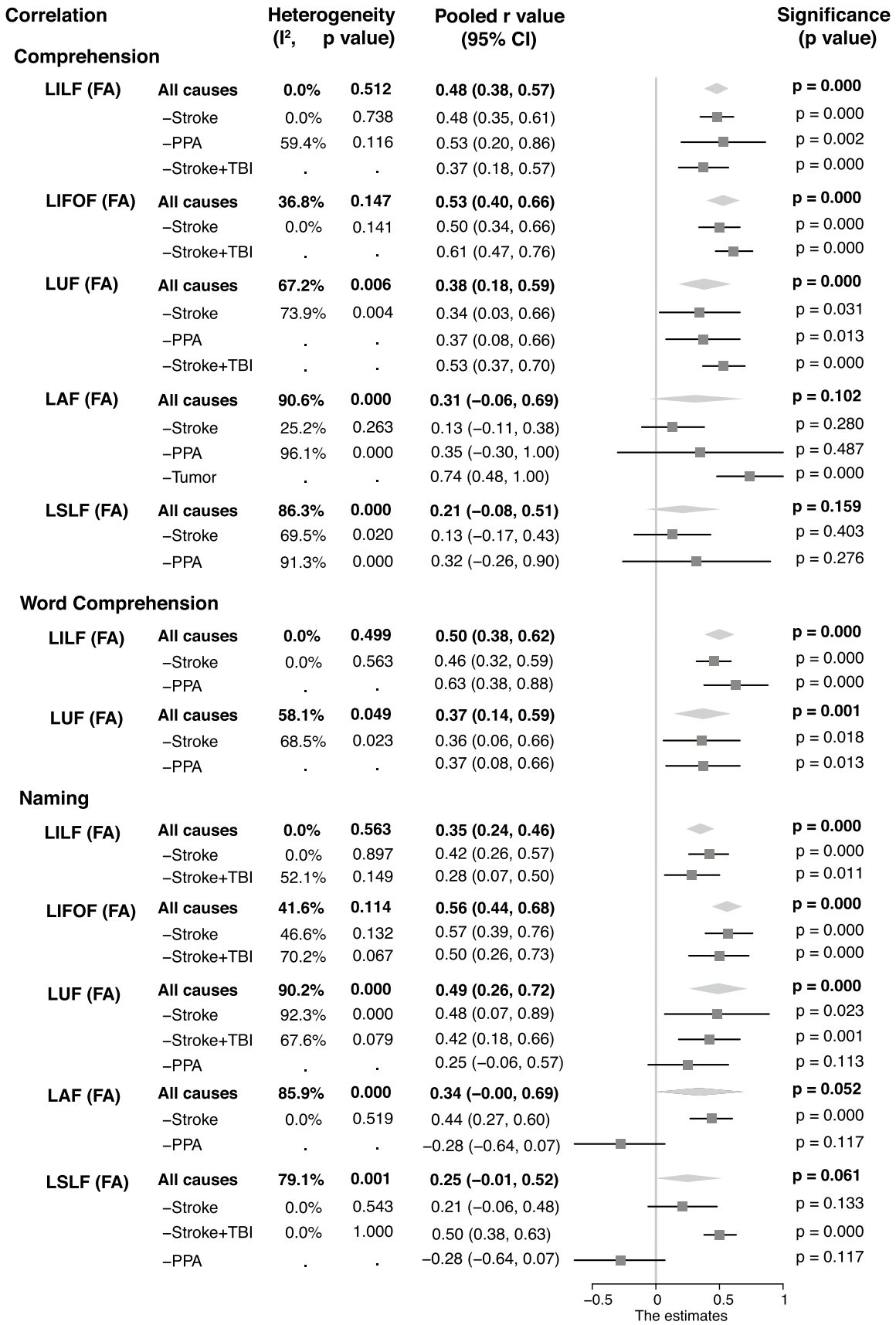


Fig. 5 Forest plot of subgroup analyses for correlations between FA and subdomains of comprehension from levels of single word, sentence comprehension, and semantic association. *Note:* Diamonds represent overall r values of correlation coefficients. FA, fractional anisotropy; CI, confidence interval; LSLF, left superior longitudinal fasciculus; LAF, left arcuate fasciculus; LIFOF, left inferior fronto-occipital fasciculus; LUF, left uncinate fasciculus; LILF, left inferior longitudinal fasciculus


Correlation
Heterogeneity (I², p value)
Pooled r value (95% CI)
Significance (p value)
Comprehension
LILF (FA) All causes 0.0% 0.512 0.48 (0.38, 0.57) p = 0.000
–Stroke 0.0% 0.738 0.48 (0.35, 0.61) p = 0.000
–PPA 59.4% 0.116 0.53 (0.20, 0.86) p = 0.002
–Stroke+TBI . . 0.37 (0.18, 0.57) p = 0.000
LIFOF (FA) All causes 36.8% 0.147 0.53 (0.40, 0.66) p = 0.000
–Stroke 0.0% 0.141 0.50 (0.34, 0.66) p = 0.000
–Stroke+TBI . . 0.61 (0.47, 0.76) p = 0.000
LUF (FA) All causes 67.2% 0.006 0.38 (0.18, 0.59) p = 0.000
–Stroke 73.9% 0.004 0.34 (0.03, 0.66) p = 0.031
–PPA . . 0.37 (0.08, 0.66) p = 0.013
–Stroke+TBI . . 0.53 (0.37, 0.70) p = 0.000
LAF (FA) All causes 90.6% 0.000 0.31 (–0.06, 0.69) p = 0.102
–Stroke 25.2% 0.263 0.13 (–0.11, 0.38) p = 0.280
–PPA 96.1% 0.000 0.35 (–0.30, 1.00) p = 0.487
–Tumor . . 0.74 (0.48, 1.00) p = 0.000
LSLF (FA) All causes 86.3% 0.000 0.21 (–0.08, 0.51) p = 0.159
–Stroke 69.5% 0.020 0.13 (–0.17, 0.43) p = 0.403
–PPA 91.3% 0.000 0.32 (–0.26, 0.90) p = 0.276
Word Comprehension
LILF (FA) All causes 0.0% 0.499 0.50 (0.38, 0.62) p = 0.000
–Stroke 0.0% 0.563 0.46 (0.32, 0.59) p = 0.000
–PPA . . 0.63 (0.38, 0.88) p = 0.000
LUF (FA) All causes 58.1% 0.049 0.37 (0.14, 0.59) p = 0.001
–Stroke 68.5% 0.023 0.36 (0.06, 0.66) p = 0.018
–PPA . . 0.37 (0.08, 0.66) p = 0.013
Naming
LILF (FA) All causes 0.0% 0.563 0.35 (0.24, 0.46) p = 0.000
–Stroke 0.0% 0.897 0.42 (0.26, 0.57) p = 0.000
–Stroke+TBI 52.1% 0.149 0.28 (0.07, 0.50) p = 0.011
LIFOF (FA) All causes 41.6% 0.114 0.56 (0.44, 0.68) p = 0.000
–Stroke 46.6% 0.132 0.57 (0.39, 0.76) p = 0.000
–Stroke+TBI 70.2% 0.067 0.50 (0.26, 0.73) p = 0.000
LUF (FA) All causes 90.2% 0.000 0.49 (0.26, 0.72) p = 0.000
–Stroke 92.3% 0.000 0.48 (0.07, 0.89) p = 0.023
–Stroke+TBI 67.6% 0.079 0.42 (0.18, 0.66) p = 0.001
–PPA . . 0.25 (–0.06, 0.57) p = 0.113
LAF (FA) All causes 85.9% 0.000 0.34 (–0.00, 0.69) p = 0.052
–Stroke 0.0% 0.519 0.44 (0.27, 0.60) p = 0.000
–PPA . . –0.28 (–0.64, 0.07) p = 0.117
LSLF (FA) All causes 79.1% 0.001 0.25 (–0.01, 0.52) p = 0.061
–Stroke 0.0% 0.543 0.21 (–0.06, 0.48) p = 0.133
–Stroke+TBI 0.0% 1.000 0.50 (0.38, 0.63) p = 0.000
–PPA . . –0.28 (–0.64, 0.07) p = 0.117
–0.5
0
0.5
1
The estimates

◂**Fig. 6** Forest plots of subgroup analyses by etiology of aphasia for correlations between FA and language domains. FA, fractional anisotropy; CI, confidence interval; LSLF, left superior longitudinal fasciculus; LAF, left arcuate fasciculus; LIFOF, left inferior fronto-occipital fasciculus; LUF, left uncinate fasciculus; LILF, left inferior longitudinal fasciculus. Diamonds represent overall r values of correlation coefficients. FA, fractional anisotropy; CI, confidence interval; LSLF, left superior longitudinal fasciculus; LAF, left arcuate fasciculus; LIFOF, left inferior fronto-occipital fasciculus; LUF, left uncinate fasciculus; LILF, left inferior longitudinal fasciculus; PPA, primary progressive aphasia; TBI, traumatic brain injury

Subgroup analyses revealed that the correlation with the FA of the left arcuate fasciculus was significant ($r = 0.48$, $p < 0.001$, 95% CI [0.32, 0.64]) with reduced heterogeneity ($I^2 = 0.0\%$, $p > 0.05$).

Syntax

As shown in Online Resource 3 (Fig. S8), the FA values of the left superior longitudinal fasciculus and arcuate fasciculus showed significant positive correlations with syntactic processing (superior longitudinal fasciculus: $r = 0.55$, $p < 0.001$, 95% CI [0.25, 0.84]; arcuate fasciculus: $r = 0.61$, $p < 0.001$, 95% CI [0.39, 0.83]). For ventral tracts (inferior fronto-occipital fasciculus, uncinate fasciculus and inferior longitudinal fasciculus), there were no significant correlations (all corrected $p > 0.05$).

Reading

As shown in Online Resource 3 (Fig. S9), the left inferior fronto-occipital fasciculus and uncinate fasciculus presented significant correlations with reading (inferior fronto-occipital fasciculus: $r = 0.34$, $p < 0.001$, 95% CI [0.17, 0.51]; uncinate fasciculus: $r = 0.28$, $p = 0.007$, 95% CI [0.08, 0.49]), and their heterogeneity was small (both $I^2 = 0.0\%$, $p > 0.05$). No significant correlations with reading were detected in the superior longitudinal fasciculus and arcuate fasciculus (both corrected $p > 0.05$).

Additional Moderator Analyses

The influence of age, sex, education, time to assess, and etiology of aphasia were investigated for the comprehension and naming domains, as these variables were represented in a sufficient number of studies (Table 2–3). Meta-regression analyses revealed that sex was the only significant moderator influencing the pooled correlation between comprehension and FA of the left arcuate fasciculus (Coefficient -4.92, 95% CI [-9.55, -0.29], $p = 0.042$). Only mean age significantly influenced the pooled correlation of naming ability with FA of the left superior longitudinal fasciculus (Coefficient -0.04, 95% CI [-0.07, -0.01], $p = 0.028$). There were no significant moderators affecting correlation coefficients with global severity or other subdomains (Tables S5-6). The varying etiology of aphasia was not a significant moderator (Table 2–3; Table S5-6), which is consistent with the results of the subgroup analyses predefined by etiology of aphasia (Fig. 6).

Assessment of Publication Bias

The funnel plots (Online Resource 3, Fig. S10-12) and Egger's tests (Online Resource 2, Table S7) revealed no significant publication bias for correlations with comprehension, naming, and global severity (all $p > 0.1$).

Discussion

This systematic review and meta-analysis included 46 studies involving 1353 aphasic patients, thus providing a comprehensive summary. Group-wise meta-analyses show reduced FA and increased mean diffusitivity and radial diffusitivity values in the left tracts of aphasic patients compared with controls. Overall, the global severity of aphasia widely correlated with the FA of dorsal and ventral tracts, including the left superior longitudinal fasciculus and inferior fronto-occipital fasciculus. Correlation meta-analyses revealed that FA is the predominant metric with the most significant findings. Across the dual pathway tracts, the left inferior fronto-occipital fasciculus was the tract that correlated with the most language domains, including comprehension, naming, reading, and global severity. The left uncinate fasciculus and inferior longitudinal fasciculus also showed FA–comprehension associations in this study. Additionally, we detected FA–syntactic correlations in the dorsal superior longitudinal fasciculus and arcuate fasciculus tracts, apart from their relationship with repetition. Both the meta-regression and subgroup analyses indicated that the etiology of aphasia is not a critical moderator influencing the correlations.

Methodologically, FA is a suitable diffusion metric for data merging in meta-analyses. The measurement of FA is robust, even when diffusion sensitization parameters vary across different DTI studies (Li et al., 2004; Melhem et al., 2000; Zhang et al., 2004). In addition, FA is quite sensitive in detecting abnormalities in white matter. However, FA is fairly non-specific and it is therefore

Table 2 Summary of univariate meta-regression analyses for correlations between FA and composite score of comprehension

Heterogeneity factors	Left SLF		Left AF		Left IFOF		Left UF		Left ILF	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Mean age	0.00 (-0.06, 0.07)	0.920	-0.03 (-0.17, 0.11)	0.628	-0.01 (-0.04, 0.02)	0.336	0.00 (-0.06, 0.06)	0.985	0.01 (-0.01, 0.03)	0.422
Sex (male %)	-1.02 (-4.28, 2.23)	0.456	-4.92 (-9.55, -0.29)	0.042*	1.02 (-0.63, 2.68)	0.173	0.74 (-1.96, 3.44)	0.512	-0.54 (-1.67, 0.60)	0.301
Education years	0.07 (-0.16, 0.30)	0.459	0.07 (-0.25, 0.38)	0.584	-0.08 (-0.17, 0.01)	0.083	-0.07 (-0.22, 0.09)	0.326	-0.01 (-0.10, 0.08)	0.786
Time to assessment (Scan/Test)	0.01 (-0.02, 0.05)	0.385	0.01 (-0.03, 0.05)	0.672	-0.01 (-0.02, 0.00)	0.117	-0.00 (-0.02, 0.02)	0.821	0.00 (-0.01, 0.01)	0.451
Cause										
PPA	-0.05 (-1.40, 1.31)	0.929	-0.44 (-2.87, 2.00)	0.608	/	/	-0.20 (-1.58, 1.17)	0.701	0.19 (-0.28, 0.66)	0.359
Stroke	-0.45 (-1.82, 0.92)	0.412	-0.84 (-3.16, 1.47)	0.330	-0.23 (-0.60, 0.14)	0.166	-0.28 (-1.34, 0.79)	0.511	0.10 (-0.26, 0.46)	0.523

*: $p < 0.05$; *SLF*, superior longitudinal fascicle; *AF*, arcuate fascicle; *IFOF*, inferior fronto-occipital fascicle; *UF*, uncinate fascicle; *ILF*, inferior longitudinal fascicle; *PPA*, primary progressive aphasia

Table 3 Summary of univariate meta-regression analyses in the domains of naming

Heterogeneity factors	Left UF		Left IFOF		Left LILF		Left AF		Left SLF	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Mean age	-0.01 (-0.07, 0.06)	0.820	0.01 (-0.03, 0.05)	0.571	0.03 (-0.00, 0.07)	0.068	-0.03 (-0.09, 0.02)	0.135	-0.04 (-0.07, -0.01)	0.028*
Sex (male %)	-0.23 (-4.78, 4.32)	0.903	-0.17 (-3.00, 2.66)	0.879	-0.27 (-4.35, 3.81)	0.849	-1.45 (-10.06, 7.17)	0.630	1.67 (-1.17, 4.51)	0.158
Education years	-0.14 (-0.38, 0.10)	0.197	-0.00 (-0.18, 0.17)	0.950	0.08 (-0.08, 0.23)	0.214	/	/	0.05 (-0.35, 0.46)	0.631
Time to assessment (Scan/Test)	-0.01 (-0.05, 0.04)	0.576	0.01 (-0.02, 0.03)	0.517	0.01 (0.00, 0.02)	0.070	/	/	-0.01 (-0.06, 0.04)	0.532
Cause										
PPA	-0.04 (-3.28, 3.21)	0.558	/	/	/	/	/	/	-0.84 (-1.79, 0.11)	0.062
Stroke	-0.42 (-2.15, 2.99)	0.637	/	/	/	/	/	/	-0.33 (-1.09, 0.42)	0.197
Stroke + TBI	/	/	-0.34 (-1.36, 0.67)	0.358	-0.39 (-1.05, 0.27)	0.157	/	/	/	/

*: $p < 0.05$; *UF*, uncinate fascicle; *IFOF*, inferior fronto-occipital fascicle; *ILF*, inferior longitudinal fascicle; *AF*, arcuate fascicle; *PPA*, primary progressive aphasia; *TBI*, traumatic brain injury

necessary to combine FA with other metrics and interpret results with caution (Alexander et al., 2007). In this study, reduced FA accompanied by a rising radial diffusitivity indicates decreased myelin integrity in patients with aphasia (Basser & Jones, 2002; Hulkower et al., 2013). More detailed microstructural properties should be supplemented by fiber-specific metrics such as fibre density and fibre cross-section, especially in the crossing-fiber regions (Raffelt et al., 2017).

The prominent dual-pathway language model proposes roles of major tracts including the ventral superior longitudinal fasciculus, arcuate fasciculus, inferior fronto-occipital fasciculus, and uncinate fasciculus (Friederici & Gierhan, 2013). Overall, the AQ widely correlated with dorsal and ventral tracts, including the superior longitudinal fasciculus and inferior fronto-occipital fasciculus, in our study. Considering that the AQ measures global severity of aphasia, this finding supports the opinion that the maintenance of speech depends on the interaction between dorsal and ventral tracts (Cloutman, 2013).

The architecture-function correlations shown in this analysis are consistent with previous models, though there are some differences. For the dorsal pathway, current language models have reached a consensus on their multiple linguistic roles, including speech repetition and complex syntactic processes (Dick & Tremblay, 2012; Gierhan, 2013). FA–syntactic and FA–repetition correlations of the dorsal tracts in our findings are consistent with this view. Apart from the traditional sound-to-articulation role involved in speech repetition, emerging evidence supports a syntactic role of the superior longitudinal fasciculus and arcuate fasciculus, from lesion mapping and functional MRI studies (Friederici et al., 2006; Wilson et al., 2011). For the ventral semantic system, although the inferior fronto-occipital fasciculus plays a well-established role in semantic processing, the roles of the inferior longitudinal fasciculus and uncinate fasciculus are controversial. This analysis reveals that multiple ventral tracts are associated with composite score and the subdomains within the comprehension domain. This finding is in accordance with the complex architecture of the recent proposed semantic system, which consists of direct and indirect pathways (Duffau et al., 2013). The direct and essential pathway refers to the inferior fronto-occipital fasciculus, and the indirect pathway is constituted by the inferior longitudinal fasciculus and uncinate fasciculus, contributing to plurimodal semantics in parallel (Duffau et al., 2013). However, the current number of studies for each ventral tract in comprehensive subdomains was small and their results would be more convincing with more relevant studies.

Our findings reveal multi-aspect associations of the left inferior fronto-occipital fasciculus with comprehension, reading, and naming. Structurally, the inferior fronto-occipital fasciculus consists of multiple subcomponents each with different cortical terminations. The superficial and deep layers subserve semantic processing and multimodal sensory – motor integration, respectively (Martino et al., 2010; Sarubbo et al., 2013; Wu et al., 2016). The deep layer of the inferior fronto-occipital fasciculus connects the inferior occipital gyrus and fusiform area at the occipito-temporal junction, which helps explain its underlying association with reading ability (Duffau et al., 2013). Similarly, correlations between the FA of the left inferior fronto-occipital fasciculus and multiple language domains, including comprehension and naming, are also supported by a recent study in post-stroke aphasia (Zhang et al., 2018).

Friederici's model suggests that the uncinate fasciculus is related to local syntactic processes rather than semantic processes (Friederici & Gierhan, 2013). However, our findings indicate that a damaged uncinate fasciculus has broad associations with lowered comprehension, naming, and reading performance. The association between the uncinate fasciculus and multiple linguistic domains may be related to the function of its cortical terminations such as the orbito-frontal cortex and the superior temporal gyrus (Papagno et al., 2011). The orbito-frontal cortex is involved in encoding and processing names (Gorno-Tempini et al., 1998) and the pole of the superior temporal gyrus plays a role in deeper levels of semantic processing (Bonilha et al., 2017). Critical structures involved in the retrieval of word forms during the reading process are also connected by the uncinate fasciculus (Crutch & Warrington, 2003, 2004).

The inferior longitudinal fasciculus was introduced in a recent model as a major component of the ventral semantic system (Dick et al., 2014). Our findings support its associations with comprehension and naming. Given that the inferior fronto-occipital fasciculus is a well-known essential tract for the semantic system, the correlations between comprehension and the inferior longitudinal fasciculus might be related to the partially overlapped rostral terminations of inferior longitudinal fasciculus and inferior fronto-occipital fasciculus. Functionally, there is collaboration in language processing between the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus (Dick et al., 2014). The relationship between therapy-induced plasticity of the inferior longitudinal fasciculus and semantic improvements also supports this notion (McKinnon et al., 2017). With respect to naming, the inferior longitudinal fasciculus links the inferior occipital gyrus to the visual object form area located at posterior occipito-temporal junction (Duffau et al., 2013; Mandonnet et al., 2007). Additionally, there is evidence from intraoperative language mapping showing that stimulation of the inferior longitudinal fasciculus can induce visual object recognition disturbance (Gil-Robles et al., 2013).

Finally, the effects of moderators demonstrate the potential influence of demographic factors on FA–language relationships. Our analysis revealed that mean age moderated the FA–naming correlation of the left superior longitudinal fasciculus and sex influenced the correlation with comprehension. Similar results were reported by recent studies showing that age attenuated the FA–naming association of dorsal tracts (Troutman & Diaz, 2019) and that there were sex differences in FA–comprehension correlations (Jung et al., 2019). However, these statistical findings should be interpreted with caution, considering the underlying neural mechanism remains uncertain.

Overall, several strengths and implications are noticeable in this analysis. First, we reveal a critical tract, the left inferior fronto-occipital fasciculus, is associated with multiple language domains, underscoring its potential value for precise evaluation. Secondly, the pooled correlation results provide evidence of linguistic functions for tracts with historical controversy. In addition, the effects of moderators were investigated to assure the reliability of the analyses and evaluate potential influence of factors such as sex and age on linguistic processes.

Limitations

There are three noteworthy limitations in this study. First, one single tract may have multiple subcomponents and we cannot determine whether a specific linguistic domain depends differentially on particular fiber subcomponents from the current evidence. For example, few studies reported detailed results of specific branches of the superior longitudinal fasciculus, which makes the related conclusions less reliable. Secondly, most of the findings are heterogeneous, though we performed subgroup analysis and meta-regression to mitigate this effect. For instance, variation of white matter tractography protocols may introduce heterogeneity. Lastly, some studies focused on different subregions when analyzing one specific tract. Further subgroup analyses predefined by specific branches and tractography types would improve interpretability and accuracy of the conclusions. However, the number of current studies is not enough for these subgroup analyses. Emerging diffusion-weighted studies of aphasia are needed to overcome these obstacles.

Conclusions

In conclusion, three main implications emerge from this study. Firstly, we reveal the multi-aspect associations of dual-pathway tracts in aphasic patients. The left inferior fronto-occipital fasciculus shows associations with a wide range of linguistic aspects and has the potential to be an indicator for language impairment. The dorsal tract arcuate fasciculus shows multiple language associations, including repetition and syntactic processing. Secondly, this analysis supports linguistic associations of the historically disputed tracts, the inferior longitudinal fasciculus and uncinate fasciculus, regarding different comprehension subdomains. Thirdly, the varying etiology of aphasia is not a significant moderator, indicating damage of dual pathways is a common neural mechanism of language deficits. Sex has a statistically moderating effect on the correlation between comprehension and FA of the arcuate fasciculus, while mean age influences the FA-naming correlation in the superior longitudinal fasciculus. Future research should investigate the associations with fiber subcomponents and dissect crossing-fiber regions when more eligible studies emerge, which will shed light on the precise prediction of intricate language subdomains.

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Author contributions Benyan Luo designed the study, and Jie Zhang and Shuchang Zhong were responsible for literature search. Yamei Yu and Min Wu extracted data and assessed the quality. Li Zhang, Yanmei Yu and Xufei Tan checked the data and solved disagreements. Jie Zhang, Yanfei Wu and Peng Sun contributed to statistical analysis. Jie Zhang drafted the manuscript; Ruidong Cheng plotted figures, and improved the interpretation of data; Liang Zhou and Wei Zhang contributed to the manuscript revision and responded to the reviewers' comments with helpful ideas; and Juebao Li and Xiangming Ye supervised and revised it.

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Declarations

Conflict of Interest All the authors have no conflicts of interest to declare.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Local Research Ethics Committee of Zhejiang Provincial People's Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Since the data were based on previous published studies, informed consent was not required for this systematic review and meta-analysis.

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