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RESEARCH ARTICLE

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Cerebral perfusion mediated by thalamo-cortical functional connectivity in non-dominant thalamus affects naming ability in aphasia

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Abstract

Naming is a commonly impaired language domain in various types of aphasia. Emerging evidence supports the cortico-subcortical circuitry subserving naming processing, although neurovascular regulation of the non-dominant thalamic and basal ganglia subregions underlying post-stroke naming difficulty remains unclear. Data from 25 subacute stroke patients and 26 age-, sex-, and education-matched healthy volunteers were analyzed. Region-of-interest-wise functional connectivity (FC) was calculated to measure the strength of cortico-subcortical connections. Cerebral blood flow (CBF) was determined to reflect perfusion levels. Correlation and mediation analyses were performed to identify the relationship between cortico-subcortical connectivity, regional cerebral perfusion, and naming performance. We observed increased right-hemispheric subcortical connectivity in patients. FC between the right posterior superior temporal sulcus (pSTS) and lateral/medial prefrontal thalamus (lPFtha/mPFtha) exhibited significantly negative correlations with total naming score. Trend-level increased CBF in subcortical nuclei, including that in the right lPFtha, and significant negative correlations between naming and regional perfusion of the right lPFtha were observed. The relationship between CBF in the right lPFtha and naming was fully mediated by the lPFtha-pSTS connectivity in the non-dominant hemisphere. Our findings suggest that perfusion changes in the right thalamic subregions affect naming performance through thalamo-cortical circuits in post-stroke aphasia. This study

highlights the neurovascular pathophysiology of the non-dominant hemisphere and demonstrates thalamic involvement in naming after stroke.

KEYWORDS
cerebral blood flow, functional connectivity, naming, poststroke aphasia, thalamo-cortical circuits, thalamus

1 | INTRODUCTION

1.1 | Naming and related neural networks

Naming is a linguistic process consisting of attaching a lexical label to an object or concept, an essential feature of speech production as well as a fundamental ability for efficient communication (Kreutzer, DeLuca, & Caplan, 2018). It comprises a series of distinct cognitive processes, including visual perception, semantic processing, lexical selection, retrieval of phonologic or orthographic representations, and motor output planning and execution (Hillis, 2010; Johnson, Paivio, & Clark, 1996; Kohn & Goodglass, 1985; Levelt, 1999). The naming difficulty is reported virtually in all types of aphasia (Kreutzer et al., 2018; Nozari, Kittredge, Dell, & Schwartz, 2010). The complexity of the neural process and network substrates underlying naming may contribute to its susceptibility to a variety of brain pathologies, including cerebrovascular and neurodegenerative diseases (Bayles & Tomoeda, 1983; Gleichgerrcht, Fridriksson, & Bonilha, 2015; Hillis, 2010).

The neural substrate of naming processing is localized in specific networks in the left peri-Sylvian cortex, including Broca's area, the posterior temporal gyrus, motor cortex, posterior midfrontal gyrus, as well as bilateral fusiform regions and anterior temporal lobes (Gleichgerrcht et al., 2015; Lubrano, Filleron, Demonet, & Roux, 2014). These cortical networks are distributed but well-organized: object perception within fusiform regions, phonological working memory in the primary auditory region, semantics in the anterior temporal lobe, lexical retrieval in more posterior areas in the left temporal and temporal–parietal junction, and fluency in the precentral gyrus (Gesierich et al., 2012; Gleichgerrcht et al., 2015). Emerging studies on naming impairments demonstrate that naming error types depend in part on the location of brain damage (Breining & Hillis, 2020). Lesion-symptom mapping studies demonstrated that omission errors of object naming were strongly associated with left frontal and mid-anterior temporal lobe lesions in post-stroke aphasia (Chen, Middleton, & Mirman, 2019), mapping semantic production to left anterior temporal lobe and semantic recognition to frontal deep white matter (Mirman et al., 2015; Schwartz et al., 2009). The importance of white matter structures including ventral and dorsal stream tracts for naming and its subprocesses was also indicated by tractography (McKinnon et al., 2018; Xing et al., 2018). Similar lesion correlates were revealed by a voxel-based correlational analysis in chronic stroke patients, associating phonological working memory with the primary auditory region, semantics with the anterior temporal region, and fluency with the precentral gyrus (Halai, Woollams, & Lambon Ralph, 2018). In addition, voxel-based lesion analysis indicated that the left mid-posterior middle temporal gyrus and underlying white matter were the core regions for name retrieval (Baldo, Arevalo, Patterson, & Dronkers, 2013). Evidence from several task-related activation studies supported the role of left frontal and posterior temporal areas in naming (Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010), as well as involvement of right-sided regions in patients with aphasia (Abel, Weiller, Huber, & Willmes, 2014; Raboyeau et al., 2008).

It has been recognized for decades that, in addition to classical cortico-cortical networks, subcortical regions (particularly the thalamus) and cortico-subcortical networks have a considerable impact on naming (Nadeau & Crosson, 1997), with emerging supporting literature (Akinina et al., 2019). The basal ganglia and its network are not only involved in motor control but also in cognitive modulation in naming-related activities (Gil Robles, Gatignol, Capelle, Mitchell, & Duffau, 2005; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler, 2005).

Regarding the thalamus, a "lateralized linguistic" syndrome characterized by severe anomia and little change in repetition or auditory comprehension was identified in 64% of left thalamic lesions (De Witte et al., 2011). Thalamic influence on frontal and temporal cortices may be attributed to the connectivity between prefrontal cortex and medial pulvinar nucleus, which could account for the effects of thalamic lesions on language dysfunction such as anomia (Nadeau, 2021). Previous studies found that electrical stimulation in the dorsal lateral thalamus and pulvinar could produce symptoms of object anomia and lexical memory disorders, whereas repetitive misnaming was observed under anterior ventrolateral thalamus stimulation (Fedio & Van Buren, 1975). Structurally, the medial pulvinar of the thalamus in the macaque has reciprocal connections with the superior temporal and posterior parietal cortex, which form the peri-Sylvian language cortex in humans (Jones, 2007); pathologically, thalamic lesions can lead to linguistic symptoms characterized by word-finding difficulties and paraphasias (De Witte et al., 2011; Kuljic-Obradovic, 2003); electrophysiologically, both the thalamus and language eloquent cortices, including Wernicke's area, present increased amplitude of high gamma rhythms in language tasks, indicating language processing activities (Crosson, 2019; Edwards et al., 2010; Steriade, Contreras, Amzica, & Timofeev, 1996). Moreover, the basal ganglia–thalamocortical circuitry connected with Broca's area was reported to play a role in naming processing by supporting lexical retrieval and semantic information (Ullman, 2006). However, the role of the thalamic and basal ganglia subdivisions in naming remains

unclear, and the cortico-subcortical networks that underpin naming processing are poorly understood.

1.2 | Stroke-induced reorganization of the non-dominant hemisphere

A growing body of literature recognizes the involvement of the right-hemispheric homologs in language reorganization after stroke. Upregulation of the bilateral language network with peak activation in the right homolog of the Broca area was observed at the post-stroke subacute stage (Saur et al., 2006). Extensive evidence suggests that the neural substrates of naming could rely on homotopic regions of the non-dominant hemisphere. However, whether recruitment of right hemisphere structures for language processing is beneficial or maladaptive in post-stroke aphasia is still debated (Hartwigsen & Saur, 2019; Turkeltaub, Messing, Norise, & Hamilton, 2011; Wilson & Schneck, 2021). Some neuroimaging studies supported compensatory mechanisms of right homologs in naming processing, while other literature offered contradictory findings. Some researchers detected increased functional activity of the right motor cortex (Skipper-Kallal, Lacey, Xing, & Turkeltaub, 2017b), white matter integrity alteration of the right inferior longitudinal fasciculus (Blom-Smink et al., 2020) as well as increased gray matter volume of the right temporal gyrus (Hope et al., 2017), to be all related to better naming performance in post-stroke aphasia patients. Moreover, studies that investigated therapy-induced changes in activation reported the potential role of the right-hemispheric structures in naming (Menke et al., 2009; Nardo, Holland, Leff, Price, & Crinion, 2017; van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014). Nevertheless, disagreement has emerged to propose that right hemisphere activations were associated with incorrect naming (Postman-Caucheteux et al., 2010), and preservation of right homologous language pathways was associated with poor naming recovery in patients with aphasia (Keser, Sebastian, Hasan, & Hillis, 2020). Thus, the role of the contralateral network in post-stroke naming processing, including homologs of the peri-Sylvian areas and subcortical structures, remains to be elucidated.

1.3 | Relationship between cerebral perfusion and naming

Further, the physiological basis underlying the reorganization of naming networks has not been closely investigated. Regional functional activation tends to require a greater metabolic supply, which needs the support of elevated perfusion levels (Venkat, Chopp, & Chen, 2016). Cerebral blood flow (CBF), a quantitative measure of perfusion per brain tissue and unit time, is tightly coupled to focal neural activity and relatively stable over time (Buxton & Frank, 1997; Floyd, Ratcliffe, Wang, Resch, & Detre, 2003). A recent fluorodeoxyglucose-positron emission tomography (PET) study revealed that hypometabolism of different brain regions was respectively associated with naming error types of separate processing stages, supporting the physiological contribution to naming (Catricala et al., 2020). Regarding the contralateral hemisphere, higher perfusion at baseline was regarded as a potential predictor of better neurological prognosis after stroke (Thamm et al., 2019). Another study observed remote cortical hypoperfusion and revealed a CBF-naming relationship, with greater CBF corresponding to more preserved naming performance (Robson et al., 2017). During the post-stroke recovery, the reperfusion in regions including left posterior middle temporal/fusiform gyrus and Broca's area was associated with improved naming ability (Hillis et al., 2001; Hillis et al., 2006), while regions of hypoperfusion were related to the presence and type of aphasia (Hillis et al., 2004). However, little attention has been paid to the relationship between cerebral perfusion and functional connectivity (FC) of naming networks in the non-dominant hemisphere.

1.4 | Current study

In the present study, we investigated the effects of resting-state FC and regional cerebral perfusion on naming performance in patients with post-stroke aphasia. We employed the Brainnetome Atlas (BNA) to acquire fine-grained parcellations of cortical and subcortical subregions based on both anatomical and functional connections (Fan et al., 2016). The novelty of this study lies in three aspects: (1) investigating neurovascular pathophysiology of naming by coupling perfusion and functional modes; (2) focusing on the non-dominant hemisphere; (3) targeting subcortical BNA subdivisions as network components for naming processing. We aimed to examine the relationship between the CBF and FC of right subregions, as well as their associations with naming and its subdomains. We hypothesized that the altered regional cerebral perfusion of right subcortical homologs and right cortico-subcortical FC after left-hemispheric stroke may affect the naming performance of aphasia patients. We hope that this multimodal imaging study will clarify the neural substrates of naming deficits and underlying neurophysiological basis of the non-dominant cortico-subcortical circuits during the stroke-induced reorganization.

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty-five subacute stroke patients (age: 58.6 ± 13.1 years; 7 females) were recruited from a brain medical center of the First Affiliated Hospital of Zhejiang University School of Medicine to participate in this study. The inclusion criteria were: (a) first-time onset of ischemic stroke; (b) presence of aphasia in the subacute stage; (c) left-hemisphere infarction lesion; (c) aged 18–80 years; (d) Chinese as a first language with >6 years education level; and (e) right-handedness. Exclusion criteria included: (a) pre-existing neurological or psychiatric disorders; (b) psychoactive medication or alcohol use; and (c) magnetic resonance imaging (MRI) contraindications. Twenty-six age-, sex-, and education-matched healthy volunteers (age: 54.9 ± 14.0 years; 10 females) were recruited as controls via local advertisements. Patients and controls provided written informed consent. The study

protocol and consent form were approved by the Local Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. All study procedures were performed in accordance with the tenets of the Declaration of Helsinki.

2.2 | Language and clinical assessments

All patients underwent comprehensive language assessments after enrollment using the Aphasia Battery of Chinese, a Chinese equivalent of the Western Aphasia Battery (Gao et al., 1992). The assessment was conducted by a certified examiner (J.Y.). The aphasia quotient (AQ), a composite index, was calculated to measure overall aphasia severity. Among all language domains, we extracted the total score and separate subscores of naming for this study, which respectively reflected the general naming ability, picture, color, and responsive naming subdomains. The relationships between the total naming score and subscores of naming subdomains were shown in Figure S1. Considering their results were similar and highly correlated (all $r > .900$, $p < .001$), we chose the total naming score as the representative behavioral score of the naming domain for the following analyses. Clinical information, including time post-stroke (11.6 ± 6.0 days), lesion volume (55.1 ± 50.8 mL), and type of aphasia, was also recorded (Table 1). The clinical profiles and language scores were proofed and documented by another blinded researcher (Y.Y.).

2.3 | Neuroradiological acquisition

MRI data were acquired using a 3.0-Tesla Signa HDxt 2.0 scanner (GE Healthcare, Chicago, IL). Participants kept their head still and eyes closed, and were required to stay awake and relaxed without any specific thinking during the scans. Resting-state blood oxygenation level dependent (BOLD) images were acquired using a gradient-echo echo-planar imaging sequence with the following parameters: repetition time = 2,000 ms; echo time = 30 ms; flip angle = 90°; interslice gap = 0.6 mm; 33 interleaved transverse slices; acquisition matrix = 64 × 64; field of view (FOV) = 220 × 220 mm, voxel size = 4 × 3.4 × 3.4 mm; and 180 volumes. Perfusion imaging was performed using a pseudocontinuous arterial spin labeling (ASL) sequence with a three-dimensional fast spin-echo acquisition and background suppression (repetition time = 4,560 ms; echo time = 9.8 ms; post-label delay = 1,525 ms; spiral in readout of eight arms with 512 sample points in k-space; FOV = 240 × 240 mm; acquisition matrix = 128 × 128; voxel size = 4 × 1.9 × 1.9 mm; and 36 slices with no gap). Structural T1-weighted imaging was performed using a high-resolution, three-dimensional brain volume imaging sequence (repetition time = 7.8 ms; echo time = 3.0 ms; acquisition matrix = 256 × 256; FOV = 256 mm × 256 mm; voxel size = 1 × 0.5 × 0.5 mm; flip angle = 7°; and 192 slices with no gap).

2.4 | Neuroimaging preprocessing

2.4.1 | Structural image preprocessing

Structural data preprocessing was conducted using SPM12 (Welcome Department of Imaging Neuroscience, London, UK, http://www.fil.ion.ucl.ac.uk/spm/). T1-weighted imaging preprocessing steps included reorienting the images to match the standard direction, and deletion of non-brain tissue using the brain extraction tool. T1-weighted images were segmented and a study-specific gray matter template generated using the Diffeomorphic Anatomical Registration through Exponentiated Lie algebra (DARTEL) algorithm (Ashburner, 2007).

TABLE 1 Demographic and clinical information for participants in the aphasia group and the control group ($n = 51$)

	Aphasia patients ($n = 25$) Mean ± *SD*	Healthy controls ($n = 26$) Mean ± *SD*	Statistic
Sex, male (%)	18 (72.0%)	16 (61.5%)	$\chi^2(1) = 0.628$, $p = .428$
Age (years)	58.6 ± 13.1	54.9 ± 14.0	$t(49) = 0.732$, $p = .991$
Education (years)	10.2 ± 3.6	10.3 ± 4.4	$z = -0.068$[a], $p = .946$
Time post-stroke (days)	11.6 ± 6.0	—	—
Handedness, right (%)	25 (100)	26 (100)	—
ICV (cm^3)	1,555.6 ± 156.5	1,475.7 ± 143.8	$t(49) = 1.900$, $p = .063$
Lesion volume (mL)	55.1 ± 50.8	—	—
AQ	41.2 ± 23.7 (range 14.8–89.5)	—	—
Total naming score (%)	24.7 ± 33.3	—	—
Picture naming subscore (%)	26.5 ± 35.2	—	—
Color naming subscore (%)	27.3 ± 40.2	—	—
Responsive naming subscore (%)	23.2 ± 39.9	—	—

Note: Data are shown as mean (*SD*) or number (%). Reported *p*-values from two-sample independent *t* test for age and intracranial volume, Mann–Whitney *U* test for the non-normal variable education year, and chi-squared test for male proportion and handedness.
Abbreviations: AQ, aphasia quotient; ICV, intracranial volume.
[a]z value was reported for Mann–Whitney *U* test.

2.4.2 | Resting-state functional MRI preprocessing

Preprocessing steps of functional images were conducted using a toolbox for Data Processing & Analysis for Brain Imaging (DPABI) (http://rfmri.org/dpabi) (Yan, Wang, Zuo, & Zang, 2016) in MATLAB 8.2 (R2013b) (MathWorks Inc., Natick, MA). The first 10 volumes of each subject were discarded to reach magnetization equilibrium and saturation effects. The remaining 170 volumes were corrected by the acquisition time delay among different slices. Head motion was subsequently corrected by realignment. BOLD images of 4 patients whose head motion exceeded the defined motion thresholds of 2.5 mm translations or 2.5° rotations were excluded. The frame-wise displacement (FD) was calculated to quantify volume-to-volume changes in the head position (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Nuisance covariates, including six motion parameters and their first-time derivations, average signals of the cerebrospinal fluid, white matter, and global brain, were regressed out. Friston-24 parameter regression was then performed to control the potential influence of head motion. Spike regression was further performed by regressing out the signal spike when the FD threshold of a specific volume was >0.5. With the spatial transformation matrices from DARTEL segmentation, images were registered to the study-specific template and then normalized to the standard Montreal Neurological Institute (MNI) space. Subsequently, functional images were resampled to a voxel size of $3 \times 3 \times 3\ mm^3$. Then, the BOLD signal within each voxel was band-pass filtered (0.01–0.08 Hz) to moderate the influence of low-frequency drift and high-frequency noise (Foerster, Tomasi, & Caparelli, 2005), after which detrending was conducted to remove the linear trend. Finally, Gaussian smoothing was applied to the functional images with a specified full-width at a half maximum (FWHM) of 3 mm. The number of useable BOLD volumes is 170 for all the included subjects in the analysis.

2.4.3 | ASL preprocessing

First, label images were subtracted from control images to calculate the ASL difference images. The three ASL difference images were averaged, and then the CBF maps were calculated with the proton density-weighted reference images (Xu et al., 2010). Individual ASL images were nonlinearly co-registered to a PET-perfusion template in the standard space using nonlinear transformation in SPM12. A study-specific CBF template in the standard MNI space was then generated by averaging the co-registered images. Subsequently, all individual CBF images were co-registered to the study-specific template and warped into the standard MNI space. The CBF value of each voxel was normalized by dividing the mean CBF value of the global brain (Aslan & Lu, 2010). The normalized CBF images were finally smoothed with a Gaussian kernel (8 mm FWHM).

2.5 | Neuroimaging analyses

2.5.1 | Structural analysis

The intracranial volume was calculated by the Tissue Volume module based on segmented T1-weighted data in SPM12. The lesion masks were drawn manually on high-resolution T1-weighted images using ITK-SNAP (Yushkevich et al., 2006) by two experienced neurological researchers (J.Z. and S.Z.). All subject lesion masks were binarized, and the lesion volumes of the subject lesion masks were calculated individually. To generate an overlapping lesion map, all subject binary lesion masks were normalized into the standard MNI space. The map in Figure 1 shows the stroke lesion distribution.

2.5.2 | Definition of region-of-interests related to naming

Cortical region-of-interests (ROIs) related to naming were selected by the meta-analytic engine NeuroSynth (https://www.neurosynth.org). We chose "naming" as term, and the results of an automated meta-analysis of all naming-related functional imaging studies in the NeuroSynth database were rendered as a brain activation map. Considering the hypothesis of right-hemispheric network recruitment in this study, we selected right activated area and right homologs of the left activated area in the meta-analytical association test map. Pooled activation areas of reported peak *z*-score with their MNI coordinates related to the naming domain were converted to corresponding BNA surface parcellation subregions, which were regarded as cortical ROIs.

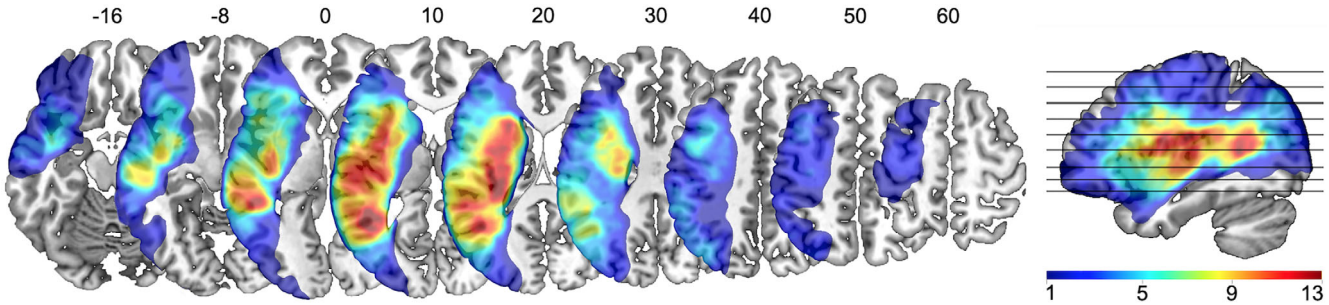

FIGURE 1 Overlap map depicting left-hemisphere lesion distributions of all aphasia patients ($n = 25$). The color bar represents the number of participants with a lesion in a given voxel between 1 and 13

Selection of subcortical ROIs was based on prior structural and functional connectivity of BNA (see details in Figure S2).

2.5.3 | ROI-wise FC analysis

Using the preprocessed functional images as input data, we extracted the BOLD signal of each ROI in DPABI. FC is measured by the Pearson's correlation coefficients for pairs of time series between each ROI for all participants using BrainNetClass (v1.0) (Zhou et al., 2020). Fisher's *z* transformation was also performed for the ROI-wise FC values to fit the normal distribution. Between-group differences of ROI-to-ROI FC *z*-values were investigated to identify significant connectivity based on BNA segmentation. Between-group comparison of the functional network was performed using the network-based statistic (NBS) Connectome (version 1.2) (Zalesky, Fornito, & Bullmore, 2010). Using NBS, family-wise error rate (FWER)-corrected *p*-values are calculated for each connection using permutation testing ($n = 5{,}000$). Subsequently, we investigated the FC-naming relationship for nodes with significant changes after NBS correction. To investigate how the subcortical subregions with altered connectivity interconnect with naming-related cortices, correlation analyses were conducted between these cortico-subcortical connectivity and naming performance.

2.5.4 | CBF alteration and naming correlations

The ROIs for the perfusion analysis were extracted from the NBS-based FC analyses that showed significant connectivity changes. ROI-wise comparisons were then performed to investigate subregions with significant CBF changes between patient and control groups. Correlation analyses were performed to identify relationships between within-ROI mean CBF and naming performance.

2.6 | Statistical analyses

2.6.1 | Group comparison and correlation

NBS-based two-sample *t* test was used for between-group comparisons of ROI-wise FC. Group differences of ROI-wise CBF were compared using general linear models in IBM SPSS Statistics for macOS (v26; IBM, Armonk, NY). Nonparametric bivariate Spearman's partial correlation analysis was performed to investigate the relationship between naming domain and ROI-wise values. The threshold of statistical significance for multiple comparisons was corrected by a false discovery rate (FDR) method with a corrected threshold of $p < .05$ (Benjamini & Hochberg, 1995; Genovese, Lazar, & Nichols, 2002). All between-group comparison and correlation analyses used age, sex, education, and stroke lesion volume as the nuisance covariates, and an additional covariate mean FD was included to moderate the effect of head motion for FC.

2.6.2 | Mediation analysis

The interactions between functional connectivity architecture and blood supply involve multiple factors (Liang, Zou, He, & Yang, 2013). Considering the perfusion alteration as the pathophysiological fundamental of stroke, altered regional CBF is reasonable to be the independent factor. The FC (i.e., the connection strength between subcortical and cortical regions) can be inferred as the bridge and the mediator between CBF and the behavioral score. To investigate whether the relationship between cerebral perfusion (independent variable) and naming performance (dependent variable) was related to cortico-subcortical connectivity (mediator), we performed mediation analyses by using model 4 of PROCESS macro (Hayes, 2018) in SPSS 26. Age, sex, education, and stroke lesion volume were used as covariates to control the influence of nuisance variables on naming abilities. Multivariable regression modeling was conducted for the mediation analysis, assessing the indirect effect of CBF on the naming domain mediated by cortico-subcortical connectivity strength, as well as the direct effect of regional CBF on naming abilities. First, we evaluated the impact of the regional CBF on the cortico-subcortical FC while controlling the nuisance covariates (Model 1 in Table S1). Subsequently, we evaluated the indirect effect of the cortico-subcortical FC while controlling the regional CBF and nuisance covariates, and the direct effect of the regional CBF while controlling the cortico-subcortical FC and nuisance covariates (Model 2 in Table S1). Bootstrapping tests with 5,000 samples and 95% confidence intervals (CIs) were used for statistical significance of mediation analyses. The indirect effect was significant if 95% CI of the mediator did not include zero.

3 | RESULTS

3.1 | Demographic and behavioral features

The demographic and behavioral features are summarized in Table 1. No significant between-group differences were reported in age, sex, level of education, or intracranial volume. Among 25 patients, 6 (24.0%) were classified as were classified as having global aphasia, 3 (12.0%) as Broca's aphasia, 7 (28.0%) as Wernicke's aphasia, 1 (4.0%) as conduction aphasia, 2 (8.0%) as anomic aphasia, 1 (4.0%) as transcortical motor aphasia, 2 (8.0%) as transcortical sensory aphasia, and 3 (12.0%) as transcortical mixed aphasia. The average AQ of all aphasia patients was 41.2 ± 23.7 (range 14.8–89.5), and the average total naming score was 24.7 ± 33.3% (range 0.0–93.5%).

3.2 | Network ROIs definition in the non-dominant hemisphere

To define the cortical ROIs for our naming study, we used the NeuroSynth's database to show the pooled results of 179 naming-related functional MRI studies (listed in Appendix S1). The cortices related to naming processing are shown in Figure 2a. Considering our

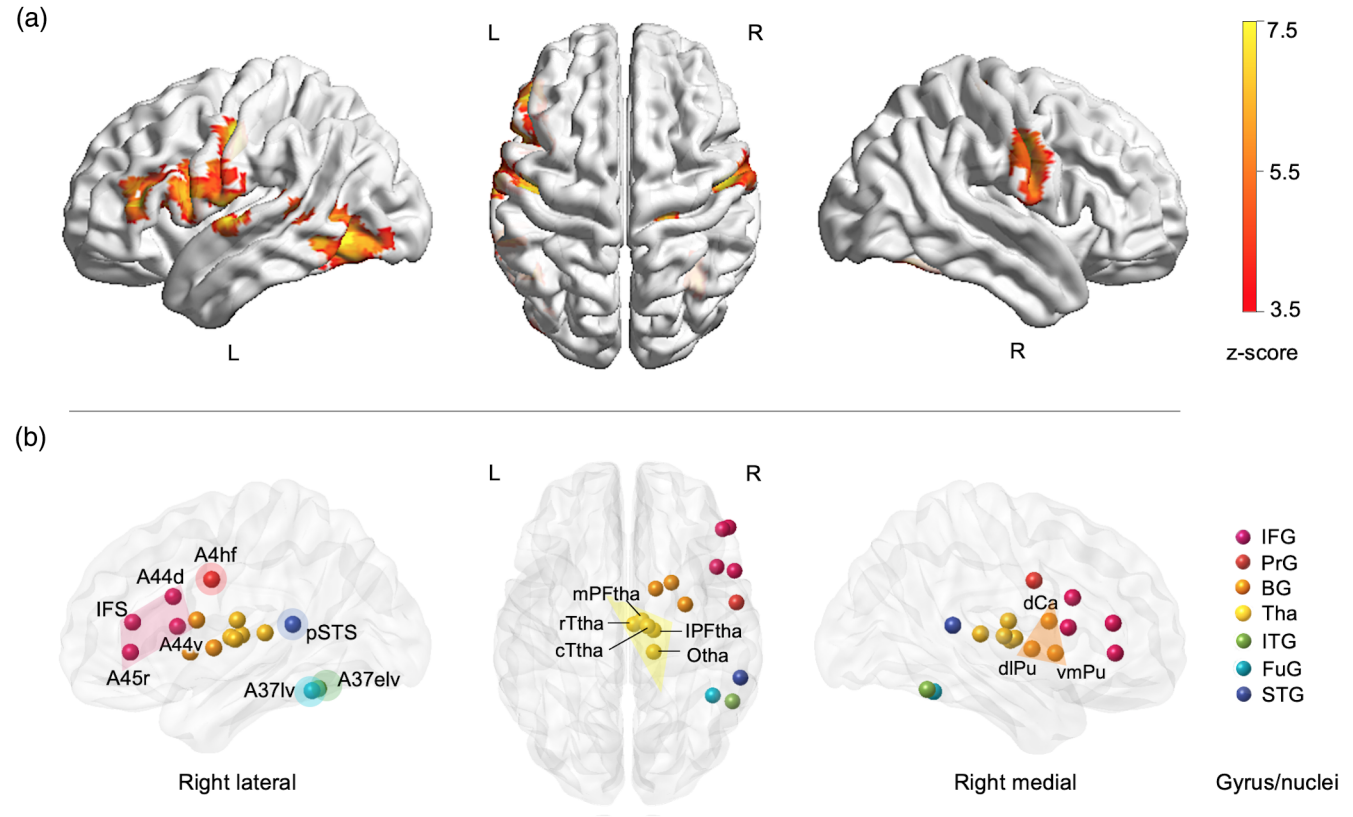

FIGURE 2 Brain networks associated with naming processing. (a) Functional map of naming obtained from NeuroSynth's database, pooling the results of 179 functional MRI studies evaluating naming. It represents meta-analytic coactivation measured by *z*-score. (b) Right hemispheric cortico-subcortical connectivity in this post-stroke naming study: right activated area and right homologs of the left activated area from (a) were selected as cortical regions of interest (ROIs) in the meta-analytical functional map, and subcortical ROIs were selected based on the prior structural and functional connections according to the BNA. cTtha, caudal temporal thalamus; lPFtha, lateral prefrontal thalamus; mPFtha, medial prefrontal thalamus; Otha, occipital thalamus; rTtha, rostral temporal thalamus; vmPu, ventromedial putamen; dlPu, dorsolateral putamen; dCa, dorsal caudate; A44d, dorsal area 44; A44v, ventral area 44; A45r, rostral area 45; A4hf, area 4 (head and face region); IFS, inferior frontal sulcus; A37lv, lateroventral area 37; A37elv, extreme lateroventral area 37; pSTS, posterior superior temporal sulcus; IFG, inferior frontal gyrus; PrG, precentral gyrus; BG, basal ganglia; Tha, thalamus; ITG, inferior temporal gyrus; FuG, fusiform gyrus; STG, superior temporal gyrus

hypothesis focused on the right-hemispheric network recruitment, we selected right activated areas and right homologs of the left activated areas in the meta-analytical functional map. The involved subregions around the right inferior frontal gyrus (homolog of Broca's area) included the dorsal area 44 (A44d), ventral area 44 (A44v), rostral area 45 (A45r), and inferior frontal sulcus (IFS), while the precentral gyrus subregion included the area 4 head and face region (A4hf). In addition, the right posterior superior temporal sulcus (pSTS) (homolog of Wernicke's area), extreme lateroventral area 37 (A37elv) of the inferior temporal gyrus, and lateroventral area 37 (A37lv) in the fusiform gyrus were also listed as potential naming-related subregions.

Regarding the subcortical ROIs in this study, subcortical nuclei with structural and functional connectivity according to the BNA were chosen, including right thalamus (mPFtha [medial prefrontal thalamus], lPFtha [lateral prefrontal thalamus], Otha [occipital thalamus], cTtha [caudal temporal thalamus], and rTtha [rostral temporal thalamus]) and basal ganglia (vmPu [ventromedial putamen], dlPu [dorsolateral putamen], and dCa [dorsal caudate]) subregions (Figure S2). Together, we constructed cortico-subcortical networks to test their potential associations with naming (Figure 2b).

3.3 | Changed connectivity of the right network in aphasia

NBS analysis of the naming-related right-hemispheric network revealed changed connectivity in patients with aphasia compared with healthy controls (Figure 3). FCs between the right mPFtha and vmPu, as well as lPFtha and vmPu, were significantly increased in the patient group (Figure S3) ($p < .05$, FWER-corrected by NBS, 5000 permutations). However, no FC between cortical and subcortical subregions was changed significantly.

3.4 | Cortico-subcortical connectivity and naming

To investigate how the subcortical subregions with altered connectivity interconnect with naming-related cortices, we performed correlation analyses between cortico-subcortical connectivity and naming scores. Figure 4 shows the significant correlations between naming and right-hemispheric connectivity. Among predefined cortico-subcortical connections, mPFtha-pSTS ($\rho = -0.707$, $p = .002$) and

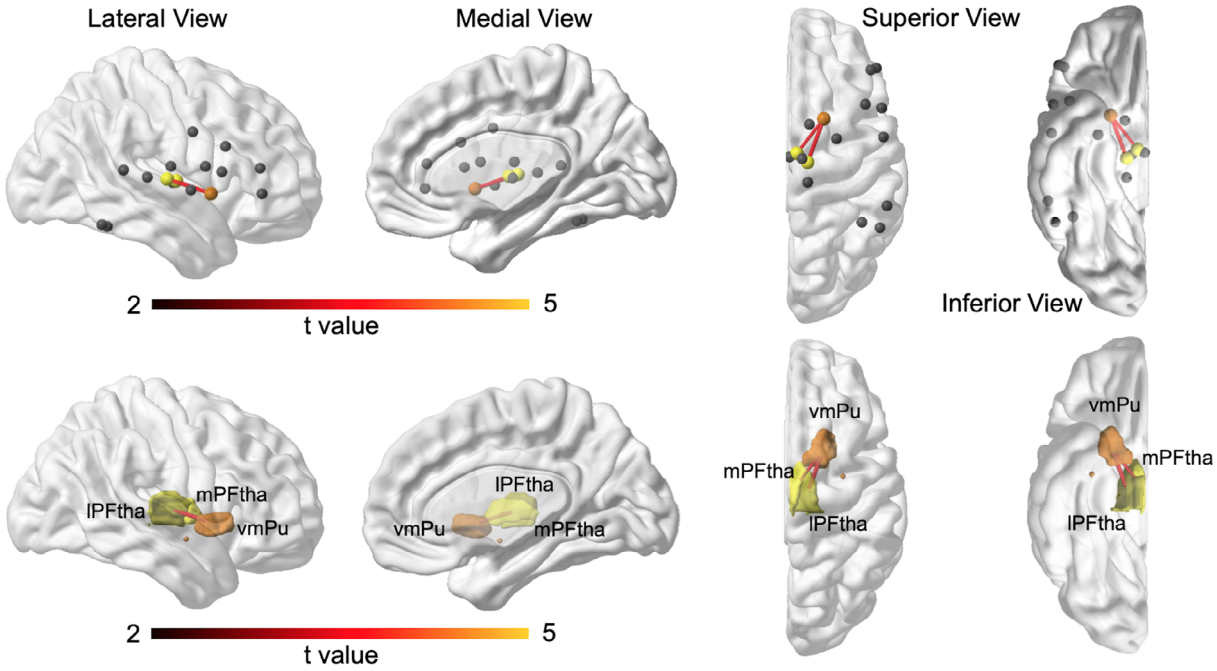

FIGURE 3 Changed functional connectivity of the naming-related right-hemispheric network in aphasia patients compared with healthy controls, controlling for age, sex, education level, and head motion. Significant increased connectivities are shown as red edges ($p < .05$, FWER-corrected by NBS, 5000 permutations). Top row: nodes with significant connectivities are colored in yellow (thalamic nuclei) and orange (basal ganglia nuclei), while other subregions are colored in gray; bottom row: subregions with significant connectivities are visualized in the form of three-dimension ROI volume

lPFtha-pSTS ($\rho = -0.684$, $p = .002$) FC *z*-values significantly correlated with the total naming score (FDR-corrected $p < .05$).

3.5 | CBF change and association with naming

Compared with controls, we found increased regional right thalamic and basal ganglia nuclei CBF in post-stroke aphasia patients (Figure 5a). Among the predefined subregions, the normalized CBF values of the right vmPu ($F = 6.170$, $p = .017$) and lPFtha ($F = 3.982$, $p = .05$) showed trend-level between-group differences.

The correlations between the regional CBF changes and naming domain are shown in Figure 5b. The mean normalized CBF value of the right lPFtha ($\rho = -0.562$, $p = .002$) significantly correlated with the total naming score (FDR-corrected $p < .05$). The mean normalized CBF values of the right vmPu and mPFtha did not show significant correlation with total naming score (FDR-corrected $p > .05$).

3.6 | Relationship between CBF, thalamo-cortical connectivity, and naming

Mediation analysis shows the relationship between the CBF, thalamo-cortical connectivity, and naming (Figure 6). The relationship between the regional CBF of the right lPFtha and general naming ability can be fully mediated by the FC between the right lPFtha and pSTS in post-stroke aphasia (indirect effect $= -32.68$, bootstrapping: $SE = 13.91$, 95% CI: -62.43 to -8.20).

However, the direct CBF effect within the right lPFtha on general naming ability was not significant (effect[c'] $= -7.73$, $SE = 18.9$, 95% CI: -48.16 to 32.71, $p = .688$). As shown in Table S1, increased CBF of the right lPFtha was associated with elevated lPFtha-pSTS FC value (decreased negative connectivity), and elevated lPFtha-pSTS FC value with worse naming performance.

Accordingly, the total effect of the regional CBF of the right lPFtha on naming abilities (including general, picture, and color naming) was mainly attributed to the indirect effect of the lPFtha-pSTS FC instead of the direct effect of within-lPFtha CBF itself.

4 | DISCUSSION

4.1 | Main findings and novelty

The main novelty of this study lies in covering the unknown gaps regarding the relationship between naming, thalamo-cortical functional connectivity, and cerebral perfusion of the right thalamic subregion. Several notable findings emerged from the current study. The first was the increased subcortical connectivity in the right hemisphere in post-stroke aphasia patients. Second, the thalamo-cortical connectivity value in the non-dominant hemisphere exhibited significant negative correlations with naming abilities, associating worse naming performance with increased functional connectivity. We also identified trend-level increased CBF in right thalamic subregions, including the lPFtha, and revealed significantly negative correlations between regional CBF and naming abilities. Lastly, mediation analysis

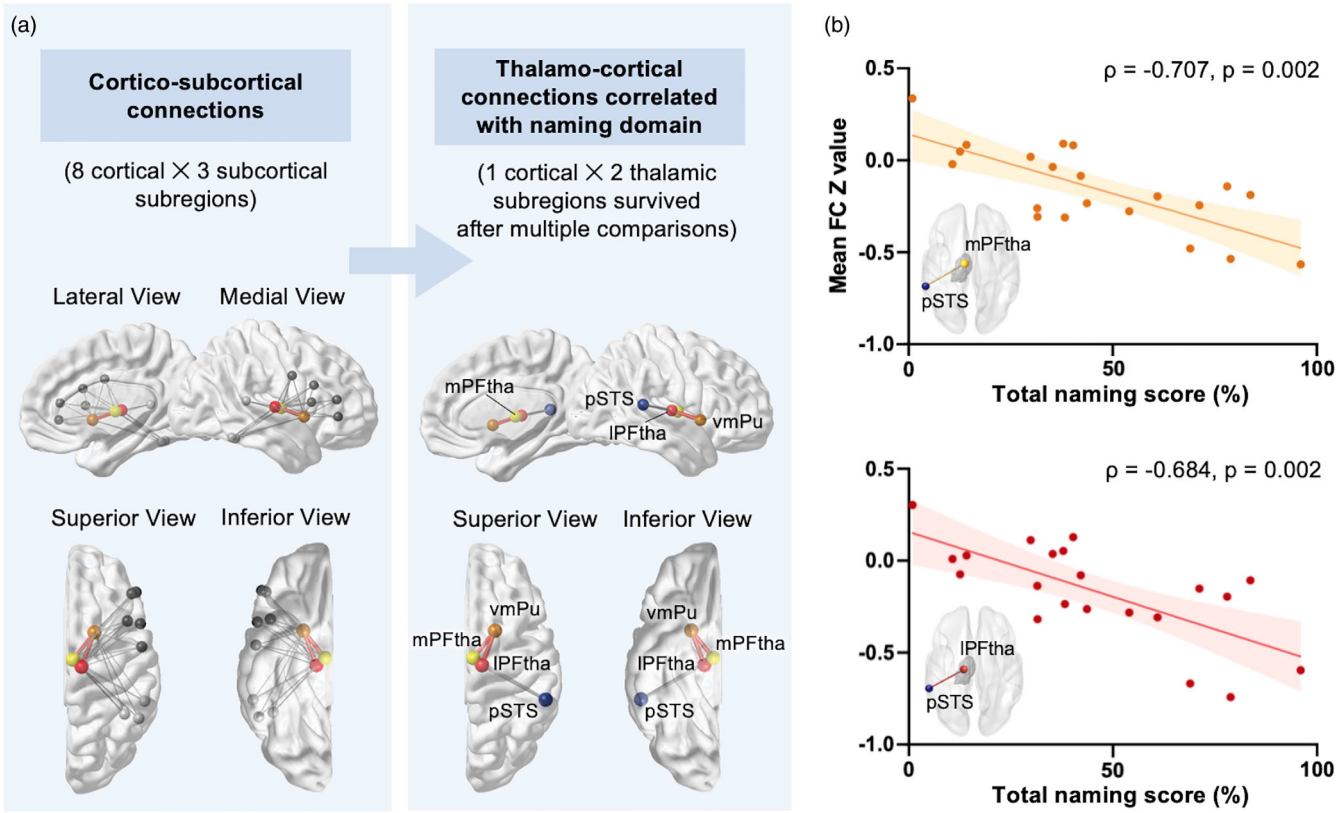

FIGURE 4 Relationships between naming domain and right hemispheric thalamo-cortical functional connectivity (FC) in aphasia patients, controlling for age, sex, education level, stroke lesion volume, and head motion. (a) Associations between naming and cortical–subcortical network (24 connections between 8 cortical and 3 subcortical subregions) was tested; the FCs between one cortical subregion (pSTS) and two thalamic subregions (lPFtha and mPFtha) show significant correlations with naming domain. (b) Scatter plots depicting the correlations between the mean FC *z*-value and total naming performance (FDR-corrected *p*-value < .05). mPFtha, medial prefrontal thalamus; lPFtha, lateral prefrontal thalamus; pSTS, posterior superior temporal sulcus; vmPu, ventromedial putamen

suggested that the relationship between CBF in the right lPFtha and naming domain is fully mediated by the connectivity between the right lPFtha and pSTS. Our results imply that the lPFtha, the non-dominant thalamic subregion, and its connection with pSTS may be related to naming difficulty severity in post-stroke aphasia.

4.2 | Naming and trans-thalamocortical circuits

This study stresses the involvement of a thalamic subregion in naming processing and indicates that its perfusion level and functional connection with the temporal cortex may influence naming performance. The thalamus, along with its radiations, has been regarded as a critical component of the lexico-semantic system (Corrivetti et al., 2019).

Previous research suggests that distinct subregions of thalamic nuclei play an important role in coupling or inhibiting spatially distributed cortical language processes (Klostermann, Krugel, & Ehlen, 2013). Using diffusion tractography, tracts between subregions of the thalamus and Broca's area have been traced in vivo (Bohsali et al., 2015). Specifically, our finding indicates that the right lPFtha is not only the thalamic subregion projecting connections to the prefrontal cortex homolog, including Broca's area, but also relays information with the pSTS. Through such transthalamic signals, thalamic neurons can be notified whether the upstream cortex has become engaged or deactivated, and thus functionally related downstream regions can be recruited or inhibited (Klostermann et al., 2013). In accordance with the present result, a previous study reported the joint thalamic and frontotemporal involvement in lexico-semantic processing during object retrieval (Assaf et al., 2006). Further, prefrontal-thalamic connectivity might interact with language-related frontotemporal cortices (Nadeau, 2021). It is in accordance with the theory of higher-order cortico-thalamo-cortical relays (Usrey & Sherman, 2019), which poses that semantic feature information could be transferred from activated cortical units to the posterior perisylvian cortex (e.g., the pSTS within Wernicke's area) to retrieve the lexical form (Crosson, 2013; Hagoort, 2006). In other words, the transthalamic higher-order relays may allow frontal subregions related to semantics (e.g., pars triangularis of anterior Broca's area) to engage higher-level semantic centers outside the prefrontal lobe (e.g., temporal lobe) to refine the lexical-semantic constructs (Crosson, 2019; Klaus & Hartwigsen, 2019).

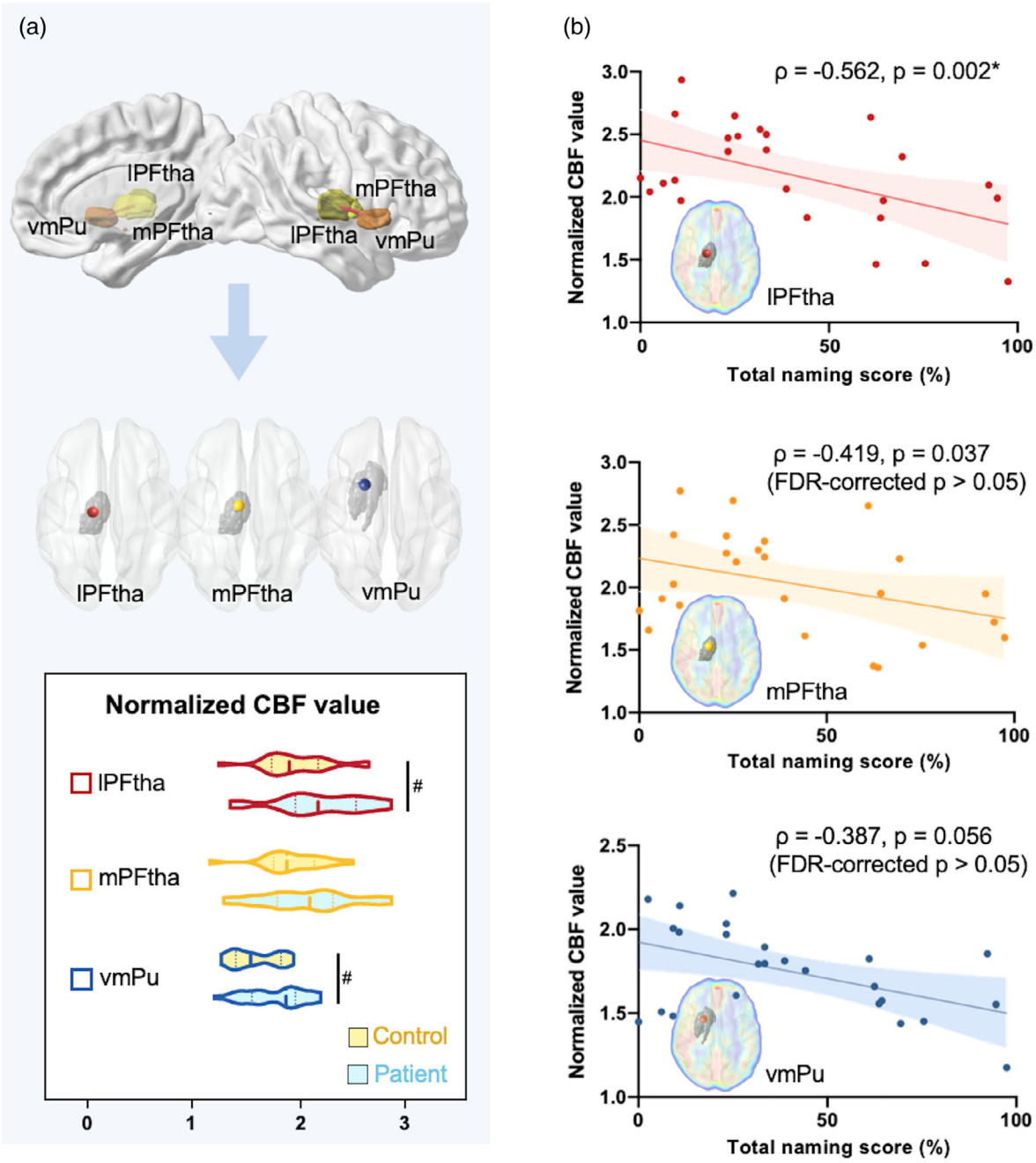

FIGURE 5 Cerebral blood flow (CBF) alterations in the subregions of interest and associations with naming performance in aphasia patients. (a) Between-group comparisons of mean normalized CBF values in subcortical subregions of interest, controlling for age, sex, and education level. (b) Correlations between mean normalized CBF value and total naming performance, controlling for age, sex, education level, and stroke lesion volume. #: uncorrected *p*-value < .05; *: FDR-corrected *p*-value < .05. mPFtha, medial prefrontal thalamus; lPFtha, lateral prefrontal thalamus; vmPu, ventromedial putamen

In addition, our results also reveal the association between naming abilities and connectivity strength with the thalamic subregion mPFtha, which receives connections from the medial prefrontal cortex. It agrees with earlier findings that the interaction between the medial dorsal thalamus and prefrontal cortex mediated naming-related retrieval functions (Van der Werf, Jolles, Witter, & Uylings, 2003), and is supported by evidence that the dorsomedial thalamus along with the prefrontal cortex is engaged in the concept or object representation for cortico-thalamic language processing (Kraut, Calhoun, Pitcock, Cusick, & Hart Jr., 2003).

4.3 | Naming and basal ganglia loops

In the current study, basal ganglia-thalamus FC values were increased in aphasia patients, especially between the right vmPu and lPFtha/

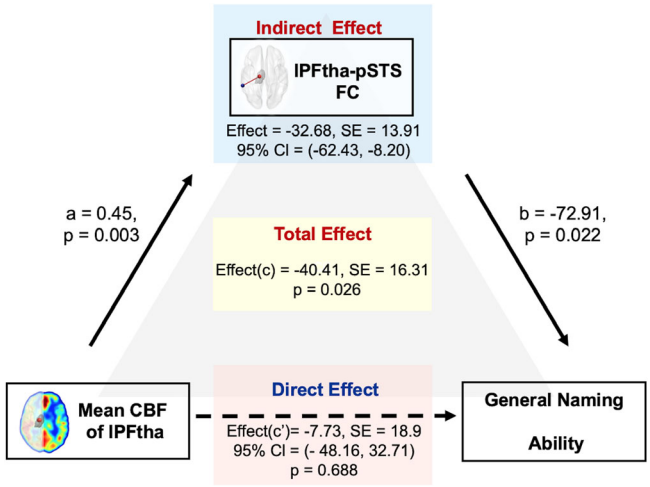

FIGURE 6 Mediation analysis among cerebral blood flow (CBF), functional connectivity (FC), and naming performance. The direct effect of mean CBF in the right lateral prefrontal thalamus (lPFtha) was nonsignificant, while the indirect (mediated) effect was significant (bootstrapping 95% CI did not include zero) through the mediating variable: the FC between the right lPFtha and pSTS. lPFtha, lateral prefrontal thalamus; pSTS, posterior superior temporal sulcus

mPFtha. Coincidentally, the right lPFtha and mPFtha are the two thalamic subregions whose connectivity with the pSTS shows significant correlations with naming abilities. Together, we postulate that the basal ganglia subregion vmPu may be involved in modulating thalamocortical circuits through basal ganglia-thalamus loops. The putamen is considered to be involved in language (Vinas-Guasch & Wu, 2017) and associated with subcortical aphasia (Kim et al., 2021). Emerging models support that basal ganglia complement cortico-thalamic language processing (Murdoch, 2001). The existence of basal ganglia thalamocortical circuits projecting to Broca's area is supported by anatomical and functional evidence (Ford et al., 2013; Ullman, 2006). However, others consider that basal ganglia-thalamus connectivity cannot be regarded as a contributor to the semantic-lexical interface, since its contribution during word-finding is not unique to semantic processing but also lexical-phonological processing (Crosson, 2019; Crosson et al., 2003). Evidence from healthy volunteers suggests that right basal ganglia activity plays a role in suppressing right frontal activity (Crosson et al., 2003). Overall, the role of basal ganglia-thalamus connections may be more like a supplementary apparatus than a dominating region for language processing.

4.4 | Right-hemispheric neurovascular reorganization and naming associations

The results of CBF and FC in our study demonstrate right-hemispheric perfusion alterations and functional reorganization in thalamic and basal ganglia subregions in aphasia patients at the subacute stage of left-hemispheric stroke, respectively. The coupling of regional CBF and remote functional connections in the thalamus has been revealed by previous research. Both hypoperfusion and functional disconnection of the right prefrontal cortex were reported in patients with thalamic infarction (Van Der Werf et al., 1999), while Zhao et al. showed that better post-stroke cognitive function was related to greater hemodynamic delay in bilateral thalamus regions, indicating longer engagement (Zhao, Lambon Ralph, & Halai, 2018).

Regarding the right-hemispheric structures, their contribution to the language domain is limited in healthy participants, and mainly involved in higher-order language functions such as context processing and additional executive control (Vigneau et al., 2011). Right subcortical structures play an inhibitory role for the right homolog activities, preventing them from interfering with language production (Crosson et al., 2003). However, the role of the non-dominant network can become different after damage to the dominant hemisphere, which could be used for language rehabilitation (Schlaug, Norton, Marchina, Zipse, & Wan, 2010). In accordance with our findings, previous research observed increased functional connectivity density of the right thalamus within a circle of thalamus-cortical language areas in post-stroke aphasia, but it did not report the relationship between altered right thalamus connectivity and language scores (Guo et al., 2019). Our findings are also consistent with other studies which associated poor naming performance with right hemisphere activations and greater preservation of contralesional pathways, though they did not address the involvement of the right thalamus (Keser et al., 2020; Postman-Caucheteux et al., 2010).

In our study, it is the regional perfusion level of the right thalamic subregions rather than that of the cortical subregions that has a total effect on naming performance. It stresses the critical role of the thalamus in naming and indicates that the effect of lPFtha-pSTS connectivity on perfusion-naming associations is unidirectional. Engagement of the right STS was detected during overt naming tasks, and over-activated right STS was associated with better naming performance in patients with aphasia (Skipper-Kallal, Lacey, Xing, & Turkeltaub, 2017a). We postulate that the hyperperfused right lPFtha and worse naming performance may have a negative relationship. It is mediated by increased connectivity of the thalamocortical circuit in patients with post-stroke naming difficulty, and thus facilitate the complementary recruitment of right temporal regions. In brief, it indicates that the non-dominant network in patients with more severe naming difficulty may upregulate right lPFtha perfusion and increases the connectivity with the right pSTS. This reorganization strategy aims at allowing the right STS to compensate in naming processing, which is modulated by the neurovascular response of the right thalamus.

4.5 | Limitations

The current study still has some limitations. First, the heterogeneity of the patient group is obvious, with varying lesion distribution and aphasia types. In the future, subgroup analysis with enlarged sample sizes is warranted. Second, naming performance and its subdomains were measured by subtests from a comprehensive battery.

Investigation of behavioral data could be more subtle with better reliability if provided with the results of naming-focused tests, including the Boston Naming Test and Philadelphia Naming Test. In addition, this study only reported behavioral and imaging findings at the subacute stage, and the long-term prognosis and reorganization remain unclear because of the cross-sectional design. Regarding the imaging quality, the number of BOLD volumes was small, and the results would be more reliable with more volumes and data. Finally, this study lacks reevaluations to reflect the dynamics of language network reorganization and aphasia recovery.

5 | CONCLUSIONS

In this study, we demonstrated that cerebral perfusion changes in the non-dominant thalamic subregions affect naming performance through the thalamo-cortical connectivity between the right lPFtha/mPFtha and pSTS in post-stroke aphasia. Our findings highlight the pathophysiology of non-dominant hemisphere recruitment, and that the right thalamic involvement of the lPFtha, from functional and vascular aspects, may underlie network reorganization for naming processing after stroke.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICS STATEMENT

This study was approved by the Local Research Ethics Committee of Zhejiang Provincial People's Hospital.

PATIENT CONSENT

Participants (controls and patients) provided written informed consent to participate in the study.

DATA AVAILABILITY STATEMENT

Anonymized data reported in this study are available from the corresponding author upon reasonable request.

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