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ORIGINAL ARTICLE

Relationship Between Perisylvian Essential Language Sites and Arcuate Fasciculus in the Left Hemisphere of Healthy Adults

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Abstract Essential language sites and the arcuate fasciculus (AF) have been extensively researched. However, the relationship between them remains insufficiently studied, especially in healthy people. Navigated transcranial magnetic stimulation (nTMS) is increasingly used in language mapping. While enjoying the advantage of non-invasiveness, it is also capable of inducing a virtual lesion in the brain. Thus, it offers the possibility of using the virtual-lesion method to study the healthy brain. This study combined nTMS and diffusion tensor imaging (DTI) tractography to investigate the relationship between essential language sites and the AF in 30 healthy right-handed volunteers. A total of 143 essential language sites were identified using nTMS, and a total of 175 AF terminations were identified using DTI tractography. Sixty-six sites had a direct correlation with the AF, accounting for 46% of the total essential language sites. Forty-seven AF terminations harbored essential language sites, accounting for 27% of the total AF terminations. Upon data rendering to the cortical parcellation system, a region-related heterogeneity of the correlation rate was found. This study provides the first data on the relationship between essential language sites and the AF in healthy adults.

Keywords Essential language site · Arcuate fasciculus · Navigated transcranial magnetic stimulation · Diffusion tensor tractography · Neuroplasticity

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Introduction

The classic theory holds that language function, which is located around the perisylvian area in the dominant hemisphere, consists of Broca's speech center and Wernicke's comprehension center. These two language centers connected by the arcuate fasciculus (AF) constitute the intact perisylvian language pathway [1]. However, the development of neuroscience has gradually unveiled a more complex language network, requiring reconsideration of the relationship between essential language sites and the AF [2]. Previous study has shown that the terminations of the AF play a critical role in language function, as protecting these areas during operations makes for a better prognosis of language function [3]. Further evidence from the functional resectability of Grade II gliomas has identified an essential connectivity represented by the main association pathways—the cortices connected by the main association pathways show more limited compensation, which indicates an essential functional role of the termination of the main association fibers [4]. By combining direct electrical stimulation (DES) and diffusion tensor imaging (DTI), another study revealed that 79% of essential language sites have a relationship with the perisylvian AF [5]. Moreover, further study revealed that the correlation rate between essential language sites and AF terminations is not consistent between anterior and posterior brain regions [6].

However, current knowledge about the relationship between essential language sites and the AF remains insufficient, mainly from three aspects. First is the method of mapping essential language sites. DES can directly reflect a causal relationship between a stimulated cortex and its function role, but it is invasive, so it is limited by the craniotomy size, mapping time, and aftercharge effect. Due to its invasiveness, the participants in the studies must be patients with lesions or functional abnormalities in the brain, which introduce confounding factors. For example, lesions in eloquent areas always result in language abnormalities and induce functional reshaping, which make the language function more complex [7]. Second are the differences in correlation rates between different brain regions. Previous studies only divided the brain into anterior and posterior areas, and so cannot reflect differences within these areas [6]. Third is the relationship itself. Relationships between essential language sites and the AF in previous studies were calculated based on essential language sites. These results can only provide the probability that an essential language site is correlated with the AF, but cannot provide the probability that an AF termination harbors an essential language site.

In the present study, essential language sites around the perisylvian areas were identified by navigated transcranial magnetic stimulation (nTMS), which has been used for language mapping in recent years. While enjoying the advantage of noninvasiveness, it is also capable of inducing a virtual lesion in the target area that can help reveal causal relationships between anatomy and function [8]. Thus, nTMS enables use of the virtual-lesion method to study healthy participants. Comparison between nTMS and DES shows a good correlation, while other methods, such as fMRI, are not always correlated with DES [9]. Picht's report confirmed that nTMS language mapping has a total sensitivity of 90.2% and a sensitivity of 100% in Broca's area [10]. Tarapore also demonstrated that nTMS language mapping has a sensitivity of 90% and a specificity of 98%, the negative predictive value even reaching 99% [11]. Recently, a study involving the resection of highly language-eloquent brain lesions purely based on nTMS language mapping before surgery showed a good language preservation rate postoperatively, confirming the reliability and effectiveness of nTMS language mapping [12]. Furthermore, with a refined protocol, including visual input initial time [13], stimulus frequency [14] and task selection in language mapping [15], nTMS can provide reliable identification of essential language sites. Then, DTI tractography provides information about the connectivity of the AF. Thus, we set out to generate probabilistic maps to reflect the heterogeneity of the relationship between essential language sites and the AF among 37 different brain regions, which would provide the first data on the relationship in healthy adults.

Materials and Methods

Participants

Thirty healthy volunteers aged 23–32 (15 males and 15 females; average age 27.1 $\pm$ 2.34 years) were recruited from Tianjin Medical University. The exclusion criteria were in accord with the general transcranial magnetic stimulation (TMS) criteria, such as having received pacemaker or cochlear implantation. Additional exclusion criteria were a history of neurological disorder, bilateral or left-handedness, developmental language deficits, and having a second mother tongue. Written informed consent was provided by the individuals before participating in the study, which was approved by the Ethics Committee of the General Hospital of Tianjin Medical University.

Image Acquisition for nTMS and DTI

MRI was performed using a 3.0-Tesla MR scanner (MR750, General Electric, Milwaukee, WI) with an 8-channel head coil. Sagittal three-dimensional T1-weighted images were acquired using a brain volume sequence with the following parameters: repetition time (TR), 7.8 ms; echo time (TE), 3.0 ms; inversion time (TI), 450 ms; field of view (FOV), 256×256 mm^2; matrix, 256×256; slice thickness, 1 mm, no gap; 188 slices. DTI data were acquired using a single-shot spin-echo echo planar imaging sequence. The DTI parameters were as follows: TR, 7100 ms; TE, 61.6 ms; matrix, 128×128; FOV, 256×256 mm^2; slice thickness, 2 mm without gap; 70 axial slices; 25 non-collinear diffusion gradients (b = 1000 s/mm^2) and one non-diffusion-weighted image (b = 0 s/mm^2).

nTMS Language Mapping

Device Description

A Magstim super Rapid2 stimulator and a 70-mm figure-of-8 coil were used in both resting motor threshold (RMT) measurements and language mapping. TMS neuronavigation software (BrainSight2.0, Rogue Research Inc., Montreal, Canada) was used for stereotactic registration and online visualization of the TMS coil position. The system error of the navigation system was <1 mm, which ensured the accuracy of language mapping. An electromyography (EMG) system (Micromed Co., Mogliano Veneto, Italy) was used to record the surface EMG signals when measuring RMT. E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA) was used for picture presentation and nTMS device triggering.

Preparation

A picture-naming task was used for nTMS language mapping because it is one of the most common tasks used in DES. It allows for the integration of visual recognition, semantic processing, lexical access, phonological encoding, and speech production at the same time [16]. A visual naming task can successfully identify resection boundaries that preserve essential language cortices [17]. A recent nTMS study also demonstrated that an object-naming task has the highest overall error rates compared with other language tasks, making it the most discriminative task [15].

All participants were given brief instructions about the task and completed a baseline test before the formal language-mapping procedure. One hundred twenty commonly-seen color pictures were used in the baseline test. Participants were instructed to name the picture with the phrase "this is a…(这是…)" in both the baseline test and the formal language mapping to distinguish speech arrest from anomia. All misnamed and unfamiliar pictures were aborted to avoid confounding factors.

The high-resolution T1 MRI series was uploaded to the neuronavigation software to reconstruct a 3-dimensional brain surface model of the participant. This anatomical scan was then co-registered to the participant's head using anatomical landmarks, and we carefully examined the accuracy of co-registration. The peeling depth of the brain was adjusted case by case to clearly expose the cortical anatomy. After peeling the brain, grids of points were designed to cover the perisylvian cortices of the left hemisphere. The gap between points was set at 5 mm. Each point was accompanied by a trajectory to guide the coil to a preset position (Fig. 1A).

Mapping Procedure

Before language mapping, the RMT of the right hand abductor pollicis brevis (APB) muscle was determined. Mapping started at the hand knob, which was recognized on the brain surface. By adjusting the position and

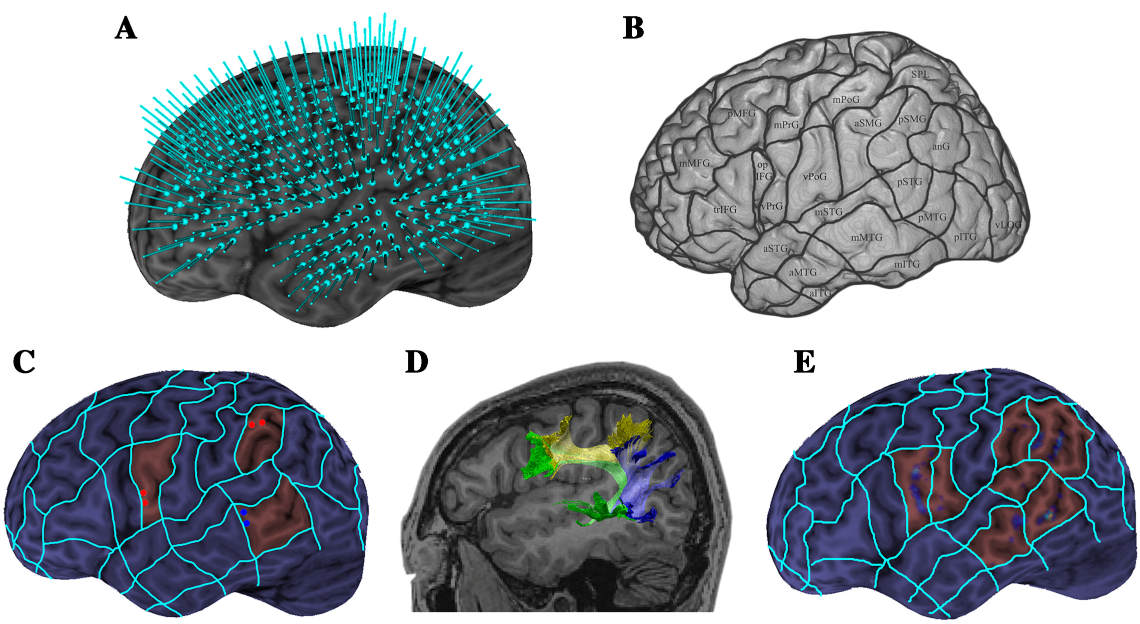


Fig. 1 Cortical mapping coverage, cortical parcellation system, language site distribution, and AF connections. **A** Individual cortical mapping coverage was designed to cover the perisylvian region. Each site was guided by a trajectory (cyan stick and ball with arrow) in order to generate the highest electric field in the target area. **B** Cortical parcellation system (CPS): abbreviations of regions related to this study are indicated (details of abbreviations in Table 1). **C** Distribution of essential language sites based on individual CPS. Individualized parcellation according to the CPS was carried out, then regions were divided into positive (red) and negative language regions (blue) depending on the positive language sites (red points, speech arrest; blue points, anomia). **D** AF reconstruction. Yellow, anterior segment; blue, posterior segment; green, long segment. **E** AF overlaid onto high-resolution T1 brain surface to reveal its cortical terminations (blue irregular flecks). The same individualized parcellation according to the CPS was carried out, then regions were divided into AF-termination regions (red) and non-AF-termination regions (blue).

Table 1 Abbreviations of anatomical cortical areas related to this study.

Abbreviation	Anatomy
aITG	Anterior inferior temporal gyrus
aMTG	Anterior middle temporal gyrus
AnG	Angular gyrus
aSMG	Anterior supramarginal gyrus
aSTG	Anterior superior temporal gyrus
mITG	Middle inferior temporal gyrus
mMFG	Middle middle frontal gyrus
mMTG	Middle middle temporal gyrus
mPrG	Middle precentral gyrus
mSTG	Middle superior temporal gyrus
opIFG	Opercular inferior frontal gyrus
pITG	Posterior inferior temporal gyrus
pMFG	Posterior middle frontal gyrus
pMTG	Posterior middle temporal gyrus
pSMG	Posterior supramarginal gyrus
pSTG	Posterior superior temporal gyrus
trIFG	Triangular inferior frontal gyrus
vPoG	Ventral postcentral gyrus
vPrG	Ventral precentral gyrus

orientation of the coil, the hotspot for the APB and the ideal orientation were identified. Then, the RMT was measured as the minimum stimulus intensity that elicited a motor-evoked potential of at least 50 μV in 5 of 10 consecutive stimulations in the right APB hotspot. After measuring the RMT of the right APB, the individual language-mapping protocol was determined by stimulating the ventral precentral gyrus (vPrG) or operculum inferior frontal gyrus (opIFG) as previously described [10].

1. After measuring the RMT of each participant, trains of repetitive transcranial magnetic stimulation (rTMS) bursts at various intensities and frequencies were delivered to the vPrG and opIFG using (a) 10 pulses at 5 Hz, 100% RMT or (b) 10 pulses at 7 Hz, 100% RMT.
2. The setup (a or b) which caused the highest error rate was identified by the impressions of the volunteer and examiner.
3. If there was no clear difference in the effect on language, the most comfortable frequency was chosen.
4. If naming was not clearly interrupted by nTMS, the intensity was increased to 110%–130% RMT and Step 1 was repeated.
5. If significant pain was reported, the stimulus intensity was decreased to 90% RMT to avoid any discomfort interfering with the naming process.

Finally, a language-mapping protocol was adopted individually, with stimulus intensity and frequency adjusted individually. The initial time of the stimulus was 0 ms after picture presentation, which was triggered by E-prime software [13]. The picture was displayed for 1 s. The inter-picture interval was 5 s, allowing time to adjust the coil to the ideal position and reduce the after-effect of the last stimulation.

The coil was moved from one point to another between the delivert of two trains of nTMS. The coil was placed in an orientation perpendicular to the sulcus and tangential to the scalp as much as possible, with the help of the navigation system. The mapping procedure was performed 3 times. Any point that showed errors more than twice was identified as a positive language site.

Classification of Language Errors

The nTMS language-mapping procedure was video-recorded for off-line analyses. A senior neurologist experienced in the differential diagnosis of aphasia, and a neurosurgeon familiar with the language errors induced by DES during awake surgery, performed the error-identification procedure. The errors were categorized into dysarthria, speech arrest, anomia, semantic error, and others, according to the DES classification [18]. Dysarthria is defined as any difficulty in articulation or vocalization (stutter, slur). Speech arrest means a complete lack of naming response due to the stimulation. Anomia means the participants were unable to name the picture but could say the introductory phrase. Semantic error means the participants appeared to provide a semantically related or associated word for the target word. Others included phonologic error, neologism, and circumlocution error, all of which showed a relatively low occurrence rate.

Distribution of Essential Language Sites

To investigate the distribution pattern of essential language sites, we used a CPS [18]. The CPS and the abbreviations of the mapped cortical regions are shown in Fig. 1B. The abbreviations are defined in Table 1. The left hemisphere of each participant was divided into 37 regions based on individual anatomical features. A region was considered a positive language region when at least one language error occurred in this area, regardless of the error type. When no positive point was identified in a region, it was considered to be a negative language area (Fig. 1C).

Arcuate Fasciculus Tractography

DTI Data Preprocessing

DTI data were preprocessed as follows. The 'eddycorrect' script of the FMRIB (Functional MRI of the Brain)

Diffusion Toolbox (http://www.fmrib.ox.ac.uk/fsl) was used to perform eddy-current correction and realignment of diffusion-weighted data using the mean of the B0 volumes as a reference. The Brain Extract tool was subsequently used to extract brain volumes from both the diffusion and high-resolution T1 volumes. Next, linear registration with 12 affine parameters was used to co-register the brain-extracted T1 volume with the B0 volume. The accuracy of the registration was carefully examined using anatomical landmarks. Then, whole-brain fiber-tracking was accomplished using DSIstudio (http://dsi-studio.labsolver.org). Deterministic tractography, using the streamline Euler approach [36], was applied with the following options: fractional anisotropy threshold, 0.18; angular threshold, 45°; step size, 0.5 mm. Whole-brain fiber tracts were reconstructed and finally transformed to the individual T1 space using the above co-registration parameters.

AF Dissection, Visualization, and Termination

The AF was dissected and visualized using Trackvis (http://www.trackvis.org). A virtual dissection of the AF in the left hemisphere was performed using approaches with one region of interest (ROI) as described previously (Supplementary Fig. S1) [37]. All three segments were reconstructed in three dimensions and visualized using illuminated stream tubes [38] (Fig. 1D). Next, the AF was saved as a .nii file and uploaded to the TMS neuronavigation software, which achieved an accurate overlap between the AF and the three dimensions of the curvilinear brain. The CPS described above was used to describe the distribution pattern of AF terminations. A region was considered an AF termination when fiber tracts projected into the region (Fig. 1E; details of procedure in Supplementary Fig. S2).

Relationship between Essential Language Sites and the AF

To investigate the relationship between essential language points and the AF, a spherical ROI was generated at the center of the nTMS-positive point coordinate using Trackvis (Fig. 2A). The radius of the sphere was set at 5 mm, considering the gap between preset points. The sphere was added as an extra ROI to the pre-existing AF fiber tracts to select those tracts that passed through the spherical ROI. When the essential language point-derived ROI contained AF fibers, the point was identified as a direct correlation point (Fig. 2B). In contrast, when the ROI had no AF fibers, the point was defined as a non-correlation point. After identifying the relationship between essential language sites and the AF, all directly correlated ROIs were toggled together, and the NOT function in Trackvis was used to calculate the fibers that did not go through any toggled spherical ROI, for the purpose of calculating the percentage of fiber tracts that had a direct correlation with the essential language sites (Fig. 2C).

Statistics

Descriptive statistics were used to report the distribution of essential language cortices and AF terminations for all participants. For each part of the CPS, the percentages of positive and negative nTMS and AF terminations were recorded. The relationship between nTMS-positive points and AF terminations was analyzed on a per-participant basis. Finally, the correlations are also presented using descriptive statistics based on the CPS.

Results

Participants

Two participants were excluded from the final analysis. One did not show repeatable language disturbance in any region around the perisylvian area. The other could not tolerate the discomfort of nTMS until we reduced the intensity to 80% of RMT, and no language disturbance

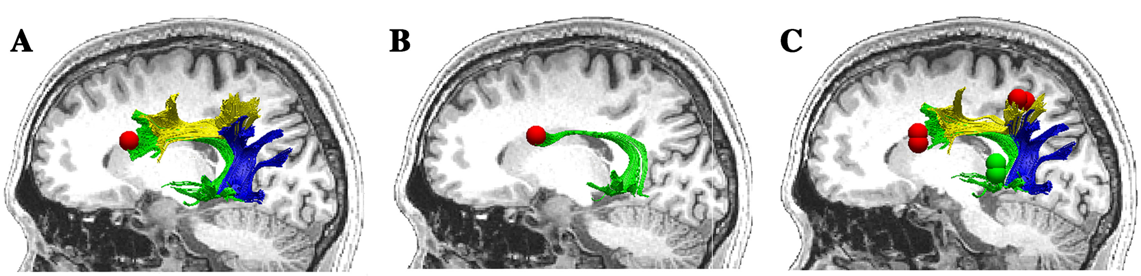


Fig. 2 Correlation between essential language sites and the AF. **A** A spherical ROI (red) with a radius of 5 mm was generated according to the coordinates of the essential language site. **B** Part of a long segment (green) of the AF passed through the spherical ROI. **C** All directly correlated ROIs (red spheres, speech arrest; green spheres, anomia) were toggled. Yellow stream, an anterior AF segment that did not pass through essential language site-derived ROIs; blue stream, a posterior AF segment that did not pass through essential language site-derived ROIs; green stream, a long AF segment that did not pass through essential language site-derived ROIs.

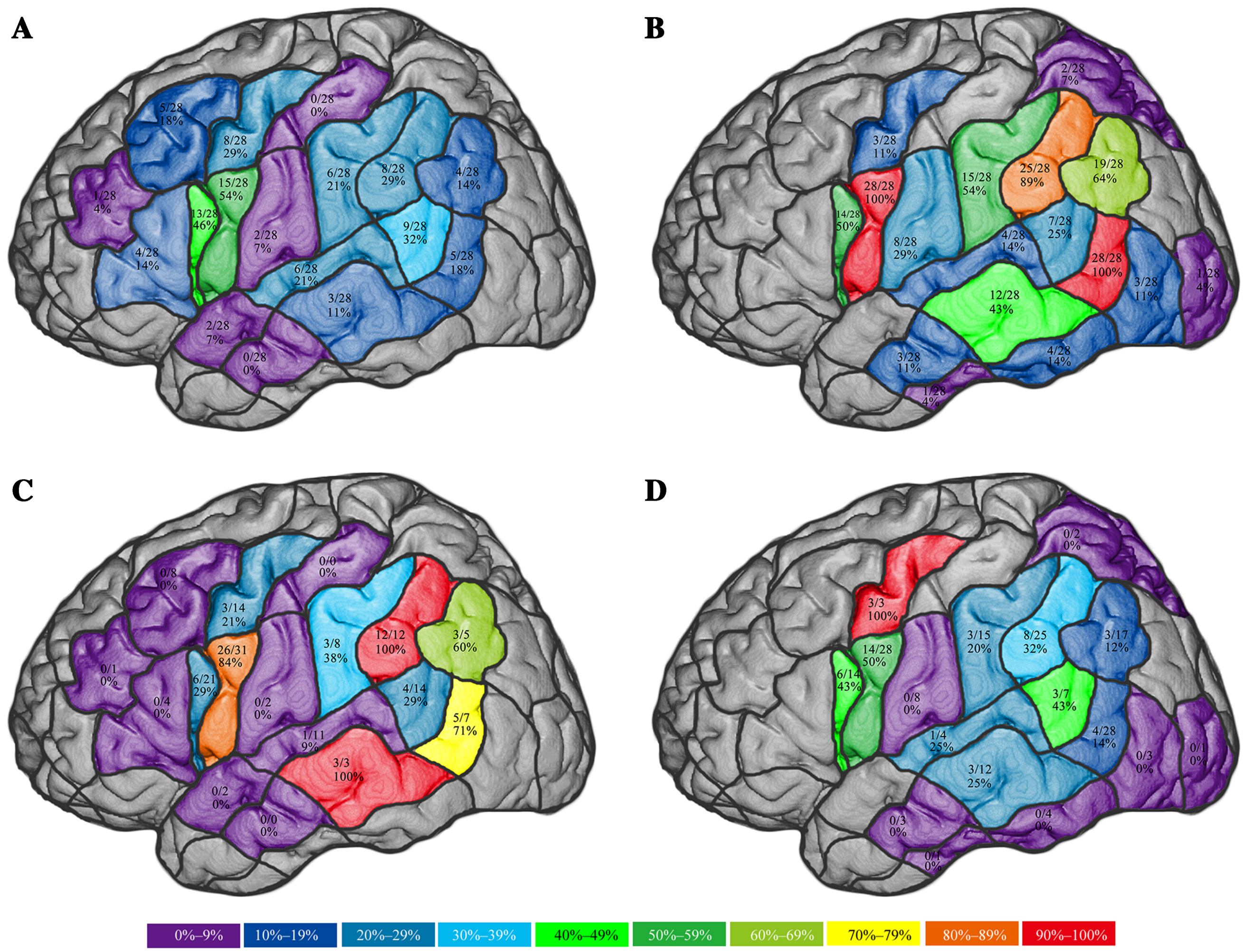


Fig. 3 **A** Distribution of essential language sites. The map illustrates the percentage of participants who showed language disturbance in each specific cortical region. **B** Distribution of AF terminations. The map illustrates the percentage of participants who had AF projections in each specific cortical region. **C** Correlation rates of essential language sites. The correlation rate of each cortical region is shown as the number of correlated positive language sites per total number of positive language sites. **D** Correlation rates of AF terminations. The correlation rate of each cortical region is shown as the number of correlated AF terminations per total number of AF terminations. Color bar indicates incidence for **A–C** and different correlation rates for **D** from low (purple) to high (red).

occurred at this intensity. The other participants showed repeatable mapping results and good tolerability of nTMS. Three reported minor headache after language mapping and recovered the next day. No participant exhibited signs of seizure. nTMS showed good tolerability with no severe side-effects.

Distribution Pattern of Essential Language Areas

A total of 143 positive language sites were identified with nTMS. A substantial variability in the number of positive language sites occurred among participants. To investigate the distribution pattern of essential language sites, all the positive sites from each individual were integrated to create a distribution map (Fig. 3A). In the frontal lobe, the vPrG (54%) and opIFG (46%) had a higher probability of harboring essential language sites than the mPrG (29%), pMFG (18%), trIFG (14%), and mMFG (4%). In the temporal lobe, the pSTG (32%) and mSTG (21%) had a higher probability of such sites than other areas. In the parietal lobe, the aSMG (21%) and pSMG (29%) had a higher probability of these sites than the AnG (14%).

Distribution Pattern of AF Terminations

A total of 175 AF terminations were identified using DTI tractography. To investigate their distribution pattern, all the terminations in each individual were integrated to create a map (Fig. 3B). In the frontal lobe, the vPrG (100%) showed the highest probability of harboring an AF anterior termination, compared with the opIFG (50%), vPoG (29%), mPrG (11%), and other areas. In the temporal lobe, the pMTG (100%) had the highest probability, compared with the mMTG (43%), pSTG (25%), mITG (14%), mSTG (14%), pITG (11%), aMTG (11%), and aITG (4%). In the parietal lobe, the pSMG (89%) and AnG (64%) had more AF terminations than the aSMG (54%).

Correlation Between Essential Language Sites and AF Terminations

Sixty-six points had a direct correlation with the AF in a total of 143 essential language sites, which accounted for 46% of the total essential language points. To reflect the correlation rate of different brain areas, the same cortical parcellation system was used (Fig. 3C). In the frontal lobe, the vPrG (84%) had a higher correlation rate than the opIFG (29%), trIFG (0%), and pMFG (21%). In the temporal lobe, the mMTG (100%) and pMTG (71%) had higher correlation rates than other regions. In the parietal lobe, the pSMG (100%) had a higher correlation rate than the aSMG (38%) and AnG (60%).

In a total of 175 AF terminations, 47 (27%) had a direct correlation with essential language sites. The CPS was used to reflect the different correlation rates among different regions (Fig. 3D). In the frontal lobe, the mPrG (100%) and vPrG (50%) had higher correlation rates than the opIFG (43%). In the temporal lobe, the pSTG (43%) had a higher correlation rate than other regions. In the parietal lobe, the pSMG (32%) had a higher correlation rate than the aSMG (20%) and AnG (12%).

In addition to investigating the correlation rates, we further quantified these correlations by calculating the counts of AF tracts that were directly correlated with essential language sites (Table 2). The result showed that 8.9% of the AF tracts had a direct correlation with essential language sites, while the remainder had no relationship with such sites.

Table 2 Percentages of direct connections of the AF.

Participant	Unconnected track counts	Total track counts	Percentage
1	3358	4181	80.3
2	5619	6464	86.9
3	2485	2512	98.9
4	2207	2467	89.5
5	1839	1890	97.3
6	2897	3158	91.7
7	441	523	84.3
8	1710	1958	87.3
9	5971	6318	94.5
10	4656	4963	93.8
11	4514	4641	97.3
12	3455	3870	89.3
13	1307	1708	76.5
14	4828	4828	100
15	2464	2792	88.3
16	3092	3495	88.5
17	6650	6755	98.4
18	4299	4800	89.6
19	3573	3928	91.0
20	2310	2434	94.9
21	3132	3641	86.0
22	3455	3870	89.3
23	4307	4708	91.5
24	1828	2038	89.7
25	2014	2196	91.7
26	4091	4325	94.6
27	2154	2392	90.1
28	4122	4122	100
Average			91.1

Discussion

Previous DES studies have suggested a difference in the number of essential language sites among different brain lobes [19]. However, the mapping range was limited by craniotomy size, which could induce selection bias. In the present study, the probabilistic distribution map of essential language sites generated from each participant's intact perisylvian area, which was not influenced by such selection bias, confirmed an unbalanced distribution pattern of essential language sites among the frontal (57%), temporal (26%), and parietal lobes (17%).

Moreover, in the frontal lobe, the essential language sites were mainly located in the vPrG, opIFG, pMFG, and mPrG. This result confirms the importance of the inferior frontal gyrus and ventral precentral gyrus in language function, and reveals a distinction between different languages compared with previous studies [19, 20]. In our study, the probability of essential language sites was similar in the vPrG (54%) and opIFG (46%). In French speakers, the vPrG (83%) has a higher probability than the opIFG (4%) [20]. Thus, the opIFG in Chinese speakers has a higher probability of harboring essential language sites than in French speakers, indicating a crucial role of opIFG in Chinese. In addition to the difference within the inferior frontal gyrus, the posterior parts of the middle frontal gyrus (pMFG and mPrG) also presented a concentration of essential language sites. Although the probabilities were not as high as the inferior frontal gyrus, it was still responsible for essential language functions in almost half of participants (46%). Therefore, we suggest the essential language function of Chinese has two foci in the frontal lobe, one in the posterior inferior frontal gyrus and the other in the posterior middle frontal gyrus.

The temporal lobe has been suggested to have complex functions, which include sound, speech, and semantic processing. These functions are distributed in a wide area across the anterior to posterior temporal lobe [21, 22]. However, in our study the probability of language sites in the temporal lobe was lower than in the frontal lobe. Instead of a dispersed distribution across the temporal lobe, the essential language sites were mainly concentrated in the pSTG, mSTG, and pMTG. Similarly, a DES study has suggested a small number of language sites in the temporal lobe, predominantly located in the pSTG and pMTG [19]. The contradictory conclusions may be attributed to differences in research methods between studies. Those that support a wide distribution of language sites in the temporal lobe have always used observation-based methods. In contrast, our study and the DES study used blocking-based methods. Therefore, it can be postulated that, in the temporal lobe, the essential language sites are restricted both in number and in location, while the language sites are broadly located throughout the temporal lobe, assisting in the language process.

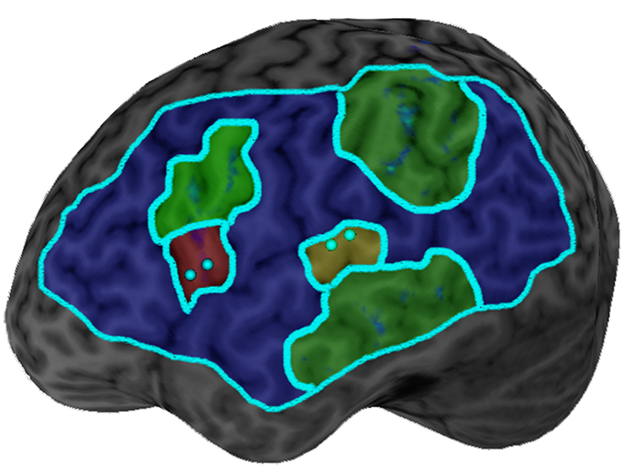
Unlike the frontal and temporal lobes, the parietal lobe is not considered a classic language area. However, the inferior parietal lobe appears to be involved in some language tasks that require memory [23]. Evidence from DES also suggests its essential functional role in language [24]. In the present study, we confirmed the essential role of the inferior parietal lobe in some participants and revealed that its essential language sites were mainly distributed in the SMG.

AF is the dorsal stream for language and plays an essential role in language function [25–27]. The AF terminates mainly in perisylvian areas. However, the distribution pattern of AF terminations was poorly understood. With a CPS system, we calculated the distribution rates of the AF in different regions. Contrary to the classical view that the AF terminates in Broca's area, it has been broadly reported that its anterior termination is most often located in the ventral precentral gyrus [28, 29]. Similarly, our results suggested that the anterior terminations are located in the vPrG (100%) more often than in the opIFG (50%) and trIFG (0%). Like a previous study that combined cortex-sparing fiber dissection and DTI tractography [30], the present study also provided an intact distribution map of AF terminations, including those in the frontal, temporal, and parietal lobes. Moreover, we performed this analysis in a larger sample with a CPS, which increased the accuracy of the localization of AF terminations. Our results revealed a similar distribution pattern of terminations, presenting a high probability of AF projections to the vPrG and opIFG in the frontal lobe, the mMTG and pMTG in the temporal lobe, and the pSMG and AnG in the parietal lobe.

It has been suggested that there is a close relationship between the essential language sites and AF terminations. One DES study has provided direct evidence of that relationship and supports previous hypotheses [5]. Moreover, further study has revealed that the correlation rates between essential language sites and AF terminations are heterogeneous among brain regions [6]. However, their study only divided the brain into anterior and posterior language areas. In the present study, we divided the brain into 37 regions using a CPS, and to our knowledge, this is the first study using a CPS to analyze the relationship between essential language sites and AF terminations. Moreover, our results illustrated this relationship in the form of two probabilistic maps. The first presented the probability of essential language sites connected with the AF among different brain regions. Substantial variability of this relationship was evident among different brain regions, indicating a role of the AF in each region. The second map reflected the probability that cortices with AF terminations harbored essential language sites in different brain regions. Compared with the first probabilistic map, the second is more useful in determining whether the AF can act as an indicator of essential language cortices when it terminates in a particular region. Our results revealed that only a few regions had a relatively high probability. Therefore, the present results indicate a high risk of misidentifying essential language sites when using AF termination alone as an indicator in the perisylvian regions, except for the mPrG, vPrG, and pSTG.

Enlightened by the finding that only a small proportion of AF terminations occur in essential language sites, we further calculated the percentage of AF tracts that pass through the essential language sites. The result showed that only a small proportion of the AF (8.9%) was correlated with essential language sites. This low percentage of "essential language fibers" signified that a large number of AF fibers are redundant, meaning that they are not involved in conducting essential language-related information. However, they may represent potential for neuroplasticity at the white-matter level. It is widely accepted that language function has great potential for neuroplasticity at the cortical level [31]. Recruitment of perilesional areas and/or remote regions within the lesioned hemisphere and/or recruitment of contralateral structures can maintain language function when the original functional area is damaged [32]. However, cortical neuroplasticity may be constrained by the main association fiber tracts [4], resulting in a poor functional prognosis in patients with extensive subcortical damage [7]. Therefore language plasticity needs both cortical reshaping and the integrity of white matter fiber tracts under the reshaping cortices. Taken together, our results suggest that the redundant AF terminations may act as potential areas for language function reshaping. Thus, such reshaping may occur at the boundaries of ipsilateral or even contralateral AF terminations.

Based on the relationship between the AF and essential language sites, brain regions can be divided into four types (Fig. 4). First are regions that had both essential language sites and AF terminations. In these regions, the AF is essential for language. To preserve the intact language function loop, surgery adjacent to these regions should protect not only the essential language cortices but also the integrity of the AF. Second are regions that had essential language sites without AF termination. In these regions, the essential language function may be conducted *via* other language-related tracts. In this situation, careful fiber reconstruction around essential language sites is needed to determine the tracts that are responsible for them. Then, surgical treatment should protect both the essential language cortices and their relevant white-matter connections. Third are regions that had AF terminations but were not essential language sites. Considering that white-matter connections constrain neuroplasticity, our results suggest that preserving these regions as much as possible could afford the chance of further functional reshaping and secondary surgical treatment. Fourth are regions that neither had essential language sites or AF terminations. A maximal resection could be implemented in these regions with a high probability of preserving language function at the cortical level. However, white-matter boundaries constituted by language-related tracts still serve as a barrier to maximal resection. Finally, instructive mapping could be carried out before surgery, to design individual treatment strategies tailored to the type of region. The probabilistic map of the correlation between essential language sites and AF terminations also provides useful information if any type of language mapping cannot be performed. It would help the neurosurgeon to determine the surgical strategy to protect language function with a high probability. Future research should combine pre-operative language mapping and fiber reconstruction with intra-operative DES mapping to decrease the mapping time and achieve a better functional prognosis for the patient. Then, a longitudinal investigation of language function could be conducted using nTMS after the operation to reveal the mechanism of language function reshaping.



Type	Essential language sites	AF terminations	Color
1	positive	positive	(red)
2	positive	negative	(yellow)
3	negative	positive	(green)
4	negative	negative	(blue)

Fig. 4 nTMS mapping coverage is outlined and further divided into different types as indicated.

This study has some limitations. We used nTMS to map the essential language sites. Although there is a good concordance between nTMS and DES when using the 2-out-of-3-rule to identify positive language sites [33], it still cannot fully replace DES. Many factors can influence the accuracy of mapping results, such as the coil orientation, angle, and the stimulation intensity and frequency. In addition, the physiological mechanism of nTMS is not fully understood [34], and the current induced by nTMS may disperse, which could influence other parts of the brain. Beyond the equipment-related confounding factors, task selection was another limitation. Neuroimaging studies suggest that different brain regions serve different language functions. The IFG, for example, has a rostro-caudal axis for syntactic, semantic, and phonologic functions [35]. Thus, to reflect the specific functions of different brain regions specific tasks might be required. Evidence from DES also suggests that region-related tasks should be selected to reveal the intact function of a specific region [36]. A recent nTMS study showed that different tasks generate different language-mapping results, which reflects a task-based language distribution pattern [37]. Regardless of the fact that picture-naming tasks can reflect multiple aspects of language function, it would be better to use region-specific tasks to identify the essential language sites.

DTI is a useful tool to investigate white-matter tracts *in vivo*, especially the well-known AF. Although numerous studies have demonstrated that the results of DTI tractography are similar to the fiber dissection findings derived from postmortems, some limitations still cast doubt on its reliability and applicability. Here, we used deterministic tractography, which produces maximum likelihood pathways, so it does not directly map anatomical connectivity but uses a mathematic algorithm. In addition, DTI not only has problems dealing with fibers merging, branching, or crossing each other but can also lead to the premature termination of a fiber, the identification of non-existent fiber tracts, or the misidentification of two or more fiber tracts as one tract [38]. More advanced mathematical algorithms and MRI sequences would help DTI to more closely approach the real situation of fiber tracts in the brain.

In conclusion, this study provides the first data on the relationship between essential language sites and the AF in healthy adults among different brain regions through the generation of two probabilistic maps. The first map unveiled the probability of AF terminations responsible for essential language sites. The second map presented the probability of an AF termination serving as an indicator of essential language sites. These maps reflect the substantial heterogeneity of the relationship between essential language sites and the AF among different brain regions. Further quantification showed that only a small part of the AF is related to essential language, indicating a great deal of AF redundancy. The white-matter fiber redundancy may represent both the potential and the limitation of neuroplasticity at the white-matter level. Finally, our results provide useful information which may influence surgical strategies within language-eloquent areas.

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