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The unique role of the frontal aslant tract in speech and language processing

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ABSTRACT

The frontal aslant tract (FAT) is a recently described intralobar tract that connects the superior and inferior frontal gyri. The FAT has been implicated in various speech and language processes and disorders, including motor speech impairments, stuttering disorders, opercular syndrome, and verbal fluency, but the specific function(s) of the FAT have yet to be elucidated. In the current study, we aimed to address this knowledge gap by investigating the underlying role that the FAT plays in motor aspects of speech and language abilities in post-stroke aphasia. Our goals were three-fold: 1) To identify which specific motor speech or language abilities are impacted by FAT damage by utilizing a powerful imaging analysis method, High Angular Resolution Diffusion Imaging (HARDI) tractography; 2) To determine whether damage to the FAT is associated with functional deficits on a range of motor speech and language tasks even when accounting for cortical damage to adjacent cortical regions; and 3) To explore whether subsections of the FAT (lateral and medial segments) play distinct roles in motor speech performance. We hypothesized that damage to the FAT would be most strongly associated with motor speech performance in comparison to language tasks. We analyzed HARDI data from thirty-three people with aphasia (PWA) with a history of chronic left hemisphere stroke. FAT metrics were related to scores on several speech and language tests: the Motor Speech Evaluation (MSE), the Western Aphasia Battery (WAB) aphasia quotient and subtests, and the Boston Naming Test (BNT). Our results indicated that the integrity of the FAT was strongly associated with the MSE as predicted, and weakly negatively associated with WAB subtest scores including Naming, Comprehension, and Repetition, likely reflecting the fact that performance on these WAB subtests is associated with damage to posterior areas of the brain that are unlikely to be damaged with a frontal lesion. We also performed hierarchical stepwise regressions to predict language function based on FAT properties and lesion load to surrounding cortical areas. After accounting for the contributions of the inferior frontal gyrus, the ventral precentral gyrus, and the superior precentral gyrus of the insula, the FAT still remained a significant predictor of MSE apraxia scores. Our results further showed that the medial and lateral subsections of the FAT did not appear to play distinct roles but rather may indicate normal anatomical variations of the FAT. Overall, current results indicate that the FAT plays a specific and unique role in motor speech. These results further our understanding of the role that white matter tracts play in speech and language.

Abbreviations: AF, Arcuate Fasciculus; AIC, Aikake Information Criterion; AOS, Apraxia of Speech; ASAF, Anterior Segment of the Arcuate Fasciculus; BNT, Boston Naming Test; CSD, Constrained Spherical Deconvolution; DTI, Diffusion Tensor Imaging; DWI, Diffusion Weighted Imaging; FAT, Frontal Aslant Tract; HARDI, High Angular Resolution Diffusion Imaging; HMOA, Hindrance Modulated Orientational Anisotropy; IFG, Inferior Frontal Gyrus; IFOF, Inferior Fronto-Occipital Fasciculus; ILF, Inferior Longitudinal Fasciculus; LL, Lesion Load; MdLF, Medial Longitudinal Fasciculus; MSE, Motor Speech Evaluation; PPA, Primary Progressive Aphasia; PWA, Participants With Aphasia; ROI, Region of Interest; SLF, Superior Longitudinal Fasciculus; SMA, Supplementary Motor Area; SPGI, Superior Precentral Gyrus of the Insula; UF, Uncinate Fasciculus; vPCG, Ventral Precentral Gyrus; WAB, Western Aphasia Battery.

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1. Introduction

Recent advances in neuroimaging analysis tools have allowed for more detailed study of the integrity of multiple white matter tracts, exploration of their role in cognitive and language processing, and exploration of the resulting functional deficits associated with white matter disconnection (Thiebaut De Schotten et al., 2020). These findings provide deeper insight into the pathology of various disorders, as well as the role these tracts play in normal speech and language functions (Chang et al., 2015; Dick et al., 2014; Fridriksson et al., 2018; Fujii et al., 2016; Griffis et al., 2017; Ivanova et al., 2016, 2021; Sierpowska et al., 2019; Turken & Dronkers, 2011). Contemporary models of language processing emphasize the importance of connections between different areas of the brain (Chang et al., 2015; Dick et al., 2014; Duffau, 2014; Mcrae et al., 2012). One example of a network model of speech and language comprises a dorsal stream for phonological processing and a ventral stream for semantic processing (Hickok & Poeppel, 2004). The core of the dorsal processing stream includes the arcuate fasciculus (AF)/superior longitudinal fasciculus (SLF), and the ventral stream centers around the inferior fronto-occipital fasciculus (IFOF) and other temporal lobe tracts such as the medial longitudinal fasciculus (MdLF) and inferior longitudinal fasciculus (ILF).

More recently, other tracts outside of these streams have been described and studied to understand their roles in emerging network models of speech and language processing (Fujii et al., 2016; Tremblay & Dick, 2016). One recently described tract is the frontal aslant tract (FAT), which runs from the supplementary motor area to the pars opercularis of the inferior frontal gyrus (IFGOp) (Catani et al., 2013; Thiebaut de Schotten et al., 2012). Since its initial description, research into the structure and function of the FAT has greatly expanded the current understanding of the tract, contributing not only to the neurocognitive understanding of the tract but also to its consideration in a clinical context (Burkhardt et al., 2021; La Corte et al., 2021). One area that the FAT has been commonly associated with includes both motor speech disorders (e.g. stuttering) and language disorders (e.g. impaired verbal fluency).

The FAT has been implicated in a number of motor speech disorders. In one study, mean diffusivity measures of both the right and left FAT were shown to be increased in adults who stutter compared with controls, likely indicating decreased integrity of the FAT in this patient population (Kronfeld-Duenias et al., 2016). On the other hand, in another study, connectivity strength of fMRI-based tractography of the right FAT (using hyperactive regions as seed masks for tractography) was shown to be positively correlated with stuttering severity, leading to a suggestion of increased robustness of a pathway that stops motor responses (Neef et al., 2018). Similarly, a diffusion tensor imaging (DTI) study in children who stutter has also shown higher integrity of the right FAT, as measured by fractional anisotropy, when compared to controls (Misaghi et al., 2018). However, in contrast to the interpretation of Neef et al. (2018), Misaghi et al. (2018) suggest that this result indicates possible right hemisphere compensation for subtle left hemisphere abnormalities. Thus, the evidence for the direction of the association between the FAT and stuttering in each hemisphere and the reason for these associations still remains unclear (Kronfeld-Duenias et al., 2016; Misaghi et al., 2018; Neef et al., 2018).

A small body of research also exists supporting speech functions of the FAT as studied in individuals with brain tumors. These studies were performed intra or post-operatively in patients who were undergoing neurosurgery for resections of left frontal gliomas. In three of these studies, intraoperative electrical stimulation was used in combination with DTI in order to determine the function of the FAT (Fujii et al., 2015; Kemerdere et al., 2016; Vassal et al., 2014). Stimulation to the FAT intraoperatively produced speech arrest in two of these studies (Fujii et al., 2015; Vassal et al., 2014) while stuttering was provoked in the third study (Kemerdere et al., 2016). In another study, the case of a patient who sustained a FAT lesion post-operatively was compared with the case of a patient who sustained an ILF lesion post-operatively (Chernoff et al., 2018). It was found that the patient with the FAT lesion demonstrated dysfluent speech but no word finding difficulty, while the other patient exhibited the reverse pattern. While current evidence supports the idea that the FAT contributes to motor speech, the details of the role the FAT plays in this process require further clarification.

With respect to speech fluency, the FAT has been implicated in patients with post-stroke aphasia and primary progressive aphasia. Halai, Woollams, and Lambon Ralph (2017) used voxel-based correlations to demonstrate an association between lesions in the insula/SMA/underlying white matter (including the FAT) and speech rate, as well as the number of words produced, during spontaneous speech. Basilakos et al. (2014) found a similar association between the FAT and spontaneous speech fluency. They found that the FAT, anterior segment of the arcuate fasciculus (ASAF), and UF were all correlated with speech fluency scores. Finally, Catani et al. (2013) and Mandelli et al. (2014) both used DTI to examine the integrity of the FAT and its relationship to fluency in patients with primary progressive aphasia and found that damage to the FAT was associated with decreased speech fluency as measured by the mean length of utterance and words per minute on the Cinderella story test.

Additionally, a number of studies showed that the FAT is related to performance on verbal fluency tasks requiring retrieval based on category and phonemic cues (Kinoshita et al., 2015; Li et al., 2017). Li et al. (2017) found that lesion load of the FAT was negatively correlated with both semantic (categorical) and phonological fluency task performance in stroke patients. Tumor resection in proximity to the FAT has similarly been shown to be associated with transient deficits on semantic and phonological fluency tasks (Kinoshita et al., 2015). Thus, it has been hypothesized that the FAT is also critical for lexical selection and retrieval because of the roles of the two cortical areas it connects (Robinson et al., 1998, 2010; Satoer et al., 2014). However, Zyryanov, Malyutina, & Dragoy (2020) were not able to demonstrate a relationship between FAT volume and lexical selection in chronic stroke patients based on a sentence completion task and picture-word inference test. However, it must be noted that these verbal fluency tasks have been shown to represent a hybrid measure of many processes such as lexical retrieval and executive functioning, as well as being correlated with motor speech measures such as oral diadochokinesia (Barbosa et al., 2017; Shao et al., 2014).

Despite the growing body of knowledge about the FAT, a number of aspects remain unclear. Prior studies largely relied on tensor-based DTI tractography to determine the structure of the FAT (Broce et al., 2015; Catani et al., 2013; Kronfeld-Duenias et al., 2016; Mandelli et al., 2014; Misaghi et al., 2018; Neef et al., 2018). However, traditional tensor-based DTI tractography has demonstrated problems with properly reconstructing crossing fibers (because it can model only one primary fiber direction per voxel), leading to incomplete tract reconstructions. Other studies have used a lesion-symptom mapping approach, which is similarly limited in its ability to estimate the true extent of damage to the tract (Basilakos et al., 2014; Li et al., 2017). Additionally, lesion-symptom mapping techniques cannot account for individual variability in tract configuration and differentiate contributions of overlapping tracts, making it harder to pinpoint the functional roles of specific white matter fiber pathways. Lastly, with respect to behavioral paradigms, previous research has typically focused on either motor speech or language functions, but not both simultaneously.

In the current study, we overcame these prior limitations by using tractography based on constrained spherical deconvolution (CSD) (Dell'Acqua et al., 2013a; Dell'Acqua et al., 2019), an advanced tractography technique that allows us to model crossing fibers, to evaluate the causal and differential contribution of the FAT to speech and language processing in a large group of individuals with post-stroke aphasia. Specifically, we analyzed whether the contributions of the FAT to speech and language performance were greater than those made

by neighboring gray matter areas, which have also been implicated in speech and language. We also evaluated the individual contributions of two distinct segments of the FAT, the medial and the lateral branches, to ascertain whether these distinct tracts both play a role in speech and language. Based on previous findings and known anatomical connections of the FAT, our hypothesis was that the FAT has a crucial role in the motor speech pathway by supporting the coordination of functions between the supplementary motor area and the inferior frontal gyrus, areas known to be involved in motor speech function. Thus, we predicted that FAT integrity would be primarily related to motor speech performance. Our second prediction was that the FAT would also be related to language measures such as verbal fluency, but not other language measures such as repetition, naming, and comprehension.

2. Methods

2.1. Participants

Thirty-three participants with aphasia (PWA) following a single left hemisphere stroke were included in the study (9 female, 24 male). The participants reported no other neurological conditions prior to the stroke, with three individuals having small lesions (<2 cm) due to prior asymptomatic events. Participants' ages ranged from 40 to 83 years old, with a mean of 64 years and standard deviation of 10 years. PWA were tested and scanned at least two months post-onset (mean = 97 months; SD = 93 months; range = 2 to 327 months). While three individuals self-reported being ambidextrous prior to stroke, with evaluation using the Edinburgh Handedness Inventory (Oldfield, 1971), all individuals demonstrated premorbid right-handed preference.

2.2. Language testing

We tested PWA on the Motor Speech Evaluation (MSE) to evaluate motor speech and determine severity ratings for apraxia of speech (AOS) and dysarthria (Wertz et al., 1984). The MSE evaluates participants' motor speech ability based on syllable and word repetition (including diadochokinesis), sentence repetition, oral reading, and picture description. For the MSE, a separate score is provided for AOS and for dysarthria. Typically a score of 0 indicates no motor speech deficit and any score $\geq$ 1 indicates a motor speech deficit. Those with a demonstrated motor speech deficit are rated from 1 to 7 based on severity with 1 indicating mild motor speech deficit and 7 indicating severe motor speech deficit. The distribution of these raw scores can be found in the Supplementary Materials (Supplementary Figure 1). However, the scoring system for patients with motor speech deficits (scores 1–7) is not standardized between patients nor between raters. For these reasons, and because our focus was whether or not the PWA had a diagnosis of AOS or dysarthria, we binarized the MSE scores for the current study. Additionally, we inverted the MSE score in order to reflect the directionality of the other speech and language tasks, with a score of 1 indicating no motor speech deficit and a score of 0 indicative of a motor speech deficit (higher score indicating better language performance). Patients received separate scores for AOS and dysarthria.

Patients' language was evaluated with the Western Aphasia Battery - Revised (WAB-R, Kertesz & Raven, 2007), which includes subtests examining Fluency, Naming, Comprehension, and Repetition. Within these subtests, Category Fluency and Information Content were also recorded as separate scores. The Fluency subtest performance is calculated based on patients' responses to a number of biographical questions and a picture description task. The Naming subtest score is based on object naming, a category fluency task (animals), a sentence completion task, and a responsive speech task. The Comprehension subtest consists of answering yes/no questions, auditory word recognition, and following sequential commands. Finally, the Repetition subtest consists of repeating words, phrases, and sentences of increasing difficulty. An Aphasia Quotient (AQ) is calculated based on scores from these subtests.

PWA were also assessed for language function with the short form of the Boston Naming Test (Kaplan et al., 2001), which includes 15 line drawings. BNT scores were missing for one patient. The BNT was included because, unlike the WAB Naming subtest, it does not count phonological paraphasias as naming errors. Thus, the BNT score is less affected by motor or pronunciation impairments. Given the emphasis on motor speech in this study, this provides an important addition to the WAB naming test.

2.3. Neuroimaging

2.3.1. Data acquisition

Brain imaging data were acquired on a Siemens Magnetom Verio 3 T MRI scanner using a 12-channel head coil. High resolution structural data was acquired using a 3D T1-weighted MPRAGE protocol with 1 mm isotropic voxel resolution: TR = 2400 ms, TE = 3.16 ms, TI = 1000 ms, flip angle = 8 degrees, FOV = 256 mm, imaging matrix = 256 × 256, acquisition time = 4.5 min. FLAIR and fast spin echo T2-weighted images were also acquired with the default Siemens pulse sequences to aid in segmentation of brain lesions. Diffusion-weighted imaging (DWI) sequences were collected with the following parameters: TR = 17600 ms, TE = 93.6 ms, flip angle = 90 degrees, b = 2000 s/mm2, 64 directions, 10 b0, FOV = 240 mm, voxel size 2 × 2 × 2 mm, 65 axial slices, bandwidth = 1812 Hz/voxel, and GRAPPA factor = 2.

2.3.2. Lesion reconstructions

The participants' lesions were traced directly onto the patient's native T1-weighted images using MRIcro/MRIcron software (Rorden & Brett, 2000). During this procedure, the T2-weighted and FLAIR images were co-registered to the T1 images to verify lesion boundaries. Then the T1 image and subsequently the binary lesion mask were normalized to an MNI template using a modified version of the unified segmentation/normalization algorithm implemented in SPM8 with cost function masking of the lesion ("Seg" toolbox in the SPM8 distribution; Crinion et al., 2007). This algorithm was customized to optimize normalization of deep white matter and ventricles by using an age relevant template and by additionally incorporating a head model (Turken et al., 2010), providing a tighter fit to the template space without distorting overall brain anatomy (Crinion et al., 2007).

2.3.3. DWI data processing

DWI data were first preprocessed: a fieldmap correction for susceptibility induced distortions was applied (FSL ver. 5.09, Jenkinson et al., 2012), followed by movement and eddy current corrections (ExploreDTI ver. 4.8.6, Leemans et al., 2009). Next, High Angular Resolution Diffusion Imaging (HARDI) deterministic tractography based on constrained spherical deconvolution was done using these parameters: ALFA – 1.8, iterations – 300, n – 0.002, r – 15, ABS thershold – 0.003, step size (mm) – 0.5, angle threshold – 35, minimal length (mm) – 50 (StarTrack beta version, Dell'Acqua et al., 2013a). Finally, manual tract dissections of the left and right FAT in native space were completed from whole brain tractograms (TrackVis ver. 0.6.1, Wang et al., 2007). A.J.Z. and M.V.I. performed the reconstructions together according to the criteria outlined below, and reconstructions were then reviewed and revised together with N.F.D. See Fig. 1 for sample segmentation.

2.3.4. Standard FAT segmentation

The FAT in both hemispheres was manually reconstructed in native space using a two-ROI stem-based approach based on placements suggested in an initial publication by Catani et al. (2012). ROIs used were disks which allowed us to capture all the fibers going through the area of the disk in a specific direction. Angle threshold was kept at the default 90 degrees for these ROI disks. All ROI disks were placed at the ends of the core white matter tract before the fibers begin to spread as they approach the cortex. ROI disks were initially placed based on the cortical regions connected by the FAT (pars opercularis of the inferior frontal

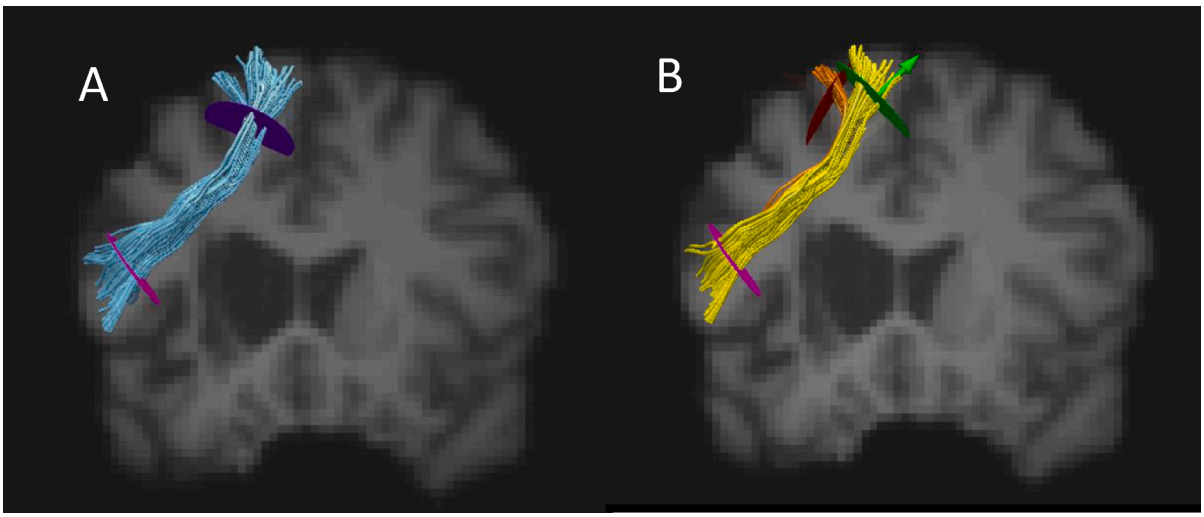

Fig. 1. Panel A – standard reconstruction of the entire FAT (blue) with ROIs in an individual. Placement of ROIs: superior frontal (purple) and inferior frontal (pink). Panel B – medial (yellow) and lateral (orange) segmentation of the FAT subcomponents with new ROIs at the dorsal endpoints. Placement of ROIs for medial–lateral segmentation: medial (green), lateral (red), and inferior frontal (pink). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

gyrus and supplementary motor/pre-supplementary motor areas) and then moved deeper to capture the underlying white matter fibers (see Fig. 1, panel A). In each individual case, ROI disk size was expanded to capture all streamlines of interest while avoiding inclusion of other nearby or aberrant fibers, thus acommodating variations among participants in brain and tract size. The ROIs were placed as follows:

- **Inferior ROI:** The inferior frontal ROI was placed in the white matter underneath the pars opercularis of the inferior frontal gyrus. In cases where the FAT was particularly large, the boundary for the ROI was within the white matter underneath the border between pars triangularis/pars opercularis anteriorly and the inferior frontal sulcus superiorly.
- **Superior ROI:** The superior frontal ROI was placed in the white matter underneath the supplementary motor and pre-supplementary motor area anterior to the pre-central sulcus. In cases where the FAT was particularly large, the posterior boundary was placed at the pre-central sulcus.

Finally, because the image processing algorithm sometimes produced aberrant and/or looping fibers that appeared to be artifacts, we placed sphere-shaped 'NOT' ROIs (which exclude fibers) as needed to remove them from the tract segmentations.

Of note, a more recent paper has described the FAT as connecting both IFG opercularis and IFG triangularis to the supplementary and pre-supplementary motor areas, rather than just the IFG opercularis as originally described by Catani (Dick et al., 2018). We attempted to additionally dissect the segment of the FAT extending from IFG triangularis. However, we were unable to reliably dissect this segment, even in those subjects with the most robust FAT tracts. Furthermore, even in the few cases when we were able to dissect this segment, it was much smaller than the segment extending from IFG opercularis. Other recent studies have additionally suggested a possible connection of the FAT to the anterior insula, although this connection has not been well-studied (Briggs et al., 2018; La Corte et al., 2021). Again, we attempted to additionally dissect a segment of the FAT extending into the anterior insula but were unable to reliably do so. Thus, we limited our segmentation of the FAT for this study to those fibers connecting IFG opercularis to the supplementary and pre-supplementary motor areas, as has been originally proposed for this tract.

2.3.5. Segmentation of two FAT subcomponents

In our prior work (Ivanova et al., 2016, 2021), we have found it insightful to look at segments of a given tract, rather than consider the entire tract alone. In our reconstructions of the FAT, we found that often the tract naturally separates into two branches to form a V-shape superiorly with one branch pointing more medially and the other branch pointing more laterally. Accordingly, we segmented the FAT into these two subcomponents – a medial and a lateral segment (Fig. 1, panel B). We again took a 2-ROI approach for each segment of the FAT and separated the two based on the superior endpoints of the tract. In cases where the branches did not separate, we counted the whole FAT as either lateral or medial depending on the directions of the endpoints. The inferior ROI was the same one used for the traditional segmentation above. The superior ROIs for these segments were duplicates of the original superior ROI that were then moved to be placed beyond the branching point of the fibers as defined below:

- **Medial Branch:** The ROI for the medial branch was placed just superior-medially to the branching point of the fibers (green disk in Fig. 1, panel B). In cases where the FAT was particularly large, we had a posterior boundary at the pre-central sulcus.
- **Lateral Branch:** The ROI for the lateral branch was placed just superior-laterally to the branching point of the fibers (red disk in Fig. 1, panel B). In cases where the FAT was particularly large, we had a posterior boundary at the pre-central sulcus.

Similarly to the traditional FAT segmentation, ROI disk size was changed as needed to capture all streamlines of interest while avoiding inclusion of other nearby or aberrant fibers, thus resulting in variation between participants depending on brain and tract size. The ROI disk was pointed in the direction of the fibers and angle threshold lowered to ~ 45 degrees to capture only fibers moving in that direction in order to avoid capturing the fibers of the other sub-segment. Again, sphere-shaped 'NOT' ROIs were placed to exclude looping and/or aberrant fibers.

2.3.6. Tract measures

For each tract segmented, volume and mean hindrance modulated orientational anisotropy (HMOA) were extracted. To account for variations in head size, normalized volume of the FAT was calculated by dividing the FAT volume (in voxels) based on tract segmentations in TrackVis by the volume (in voxels) of the corresponding hemisphere.

Greater normalized FAT volume reflects a larger tract (irrespective of brain size). HMOA is an indirect measure of tract integrity analogous to fractional anisotropy for spherical deconvolution methods (Dell'Acqua et al., 2013a). It is tract-based and derived from the absolute amplitude of each lobe of the fiber orientation distribution function and is thus sensitive to changes in diffusivity and microstructure of fibers, with higher values indicative of greater fiber integrity in a given direction. It was expected that damage to the tract would negatively impact both normalized volume and HMOA values, although to varying degrees. In cases when the tract could not be reconstructed due to the stroke lesion, the HMOA and volume of the tract were imputed to be zero.

In addition to the tract measures derived from the DWI data, we determined the lesion load to the FAT based on a standardized atlas. Lesion load to the FAT was defined as the proportion of the FAT mask taken from the Natbrainlab Atlas (Catani & Thiebaut de Schotten, 2008) thresholded at 50% that was covered by the patient's lesion in MNI space. Put simply, it was a measure of the proportion of the tract lesioned. Consequently, a higher lesion load value indicated increased damage to the FAT (e.g., a value of 0.6 indicated that 60% of the atlas-based tract was damaged). FAT lesion load was examined because it provides an alternative metric for evaluating the impact of the lesion on the FAT, which was a particularly helpful measure for participants in whom the FAT could not be reconstructed. In these instances the lesion load to the FAT provided a more graded metric reflective of the extent of damage, as opposed to normalized volume and HMOA which both had a value of zero when the FAT could not be reconstructed regardless of the amount of damage caused by the lesion.

Finally, as both cortical and subcortical areas are often affected in stroke together, the effects of damage to local cortical areas in our participants were potentially confounding the observed relationships between tract metrics and language measures. Thus, we chose to control for the effects of damage to the cortical areas surrounding the FAT, which might have similar functions to what we would expect of the FAT, to attain our goal of understanding the functional role of the FAT specifically. Accordingly, we also calculated lesion load to surrounding cortical areas to account for their contribution to speech and language deficits. These cortical areas included two parts of the inferior frontal gyrus (IFG; opercularis and triangularis) and the ventral precentral gyrus (vPCG) taken from the Harvard-Oxford Cortical Structures Atlas thresholded at 20%, as well as the superior precentral gyrus of the insula (SPGI) taken from an atlas created by AT and NFD based on prior work (Dronkers, 1996). vPCG was defined as the part of the precentral gyrus below the level of the inferior frontal sulcus. Similar to the lesion load of the FAT, lesion load to cortical areas was defined as the proportion of the cortical mask that was covered by the lesion in MNI space.

2.4. Statistical analyses

All analyses were conducted in R 4.0.2 (R Core Team, 2020). Plots were produced using ggplot2 (Wickham, 2016), partial correlations were determined using ppcor (Kim, 2015), logistic regressions were performed using bayesglm in the arm package (Gelman & Hill, 2006) and beta values were generated using QuantPsyc (Fletcher, 2012).

2.4.1. Assessing relationships between language tests and imaging data

Our first step was to assess the relationship between language scores and tract metrics of the left and right FAT. To choose appropriate covariates for this assessment, Pearson's correlations were used to determine whether age, months post onset, and lesion volume had an impact on WAB or BNT scores. Independent samples t-tests were used to explore the associations between sex and WAB or BNT scores, as well as to look at age, months post onset, and lesion volume with MSE scores. Finally, chi-squared tests were used to look at the associations between sex and MSE scores. This allowed us to determine which demographic and clinical covariates to use in the analyses.

Subsequently, for the MSE results, we determined whether tract metrics differed between individuals with and without motor speech disorders using a binomial GLM with logistic link. Separate binomial GLMs were run for each individual tract metric and each individual MSE score (separate models for apraxia and for dysarthria).

For language tasks, simple correlations and partial correlations accounting for relevant covariates were performed to identify the relationship between FAT metrics (normalized volume, HMOA, and lesion load) and the WAB (including AQ, separate subtest scores, and word fluency score) and BNT scores. To control for multiple comparisons among language tasks, we used a significance level of $\alpha^* = 0.00625$ based on the Bonferroni correction and the number of language metrics being used (0.05/8).

2.4.2. Accounting for cortical damage

To explore the observed relationships between FAT damage and speech/language tests further, we performed analyses to account for the effects of additional cortical damage in areas surrounding the FAT (IFG Opercularis, IFG Triangularis, vPCG and SPGI). For these regressions, we chose not to include lesion volume as a covariate because it is highly correlated with lesion load to cortical areas. The particular models we were interested in exploring were for those variables where we found that increased damage to the FAT across the different tract metrics was associated with decreased speech/language performance. Backwards stepwise regressions or backwards stepwise logistic regressions (for MSE models using the same Bayesian model as above for consistency) were performed to explore the ability of FAT damage to predict language outcome in the context of additional cortical damage in IFG Opercularis, IFG Triangularis, vPCG, and SPGI. A separate regression was performed for each individual tract metric (normalized Volume, HMOA, and lesion Load to the FAT). Thus, each regression performed utilized language outcome as the dependent variable and sex, lesion load to cortical areas, and tract metric as the independent variables. Model variable selection for the stepwise regressions was based on the Akaike Information Criterion (AIC) where lower AIC indicates a better model. AIC was used because it is considered the optimal model selection criterion when finding a model that best describes the data while avoiding the phenomenon of over-fitting (as opposed to adjusted R^2 which is prone to over-fitting and is used more for its predictive power). In our case, we were not attempting to develop a predictive model but rather to understand the contributions of each possible variable and to find the most parsimonious model. This allowed us to determine whether FAT metrics remained important predictors even with the inclusion of lesion load to cortical areas and data-driven selection of the most parsimonious model.

2.4.3. Exploratory analyses

The same analyses described in Sections 2.4.1 and 2.4.2 were carried out on the medial and lateral segmentations of the FAT for the whole participant cohort. Again, models were run separately for each individual tract metric with measurements for both the medial and lateral segments of the tract included in the same model. Thus, each backwards stepwise regression model in this section used language outcome as the dependent variable and sex, lesion load to cortical areas, lateral segment tract metric, and medial segment tract metric as the independent variables. Of note, we were unable to use lesion load to the FAT segment as a tract metric in these exploratory analyses because there are no individual masks for each segment to allow for calculation of overlap of lesion area with tract area.

3. Results

3.1. Screening for outliers

Prior to analysis, the behavioral and imaging data were screened for outliers (based on $>$ 3 SDs from group means). There was one outlier who had a WAB AQ of 22.8, MSE AOS rating of 7, MSE Dysarthria rating of 7, and lesion volume of 380,430 voxels. This participant was excluded

from further analyses, resulting in a total of 32 participants included in our data analysis. Boxplots are presented in Supplementary Figure 2.

3.2. Descriptive statistics

Overall, the participants demonstrated a large range of integrity of the FAT and a wide range of severity in speech and language test performance. Descriptive statistics for different tract metrics and language tests are provided in Table 1. A lesion overlay map of the lesions found in this cohort is presented in Fig. 2.

3.3. Determining covariates

We explored which demographic and lesion variables were related to the language and tract metrics. Neither age nor months post onset showed significant correlations with any of the language tasks or FAT metrics ($p > 0.05$). Lesion volume, however, showed significant correlations with WAB scores and all of the FAT metrics, as well as significant associations with MSE Apraxia of speech scores ($p < 0.05$). All these correlations were in the negative direction (increased lesion volume was associated with worse performance on language tasks or lower HMOA/normalized volume metrics), with the exception of lesion load (increased lesion volume was related to increased lesion load). Sex also showed significant associations with the WAB Comprehension, Naming, and Word Fluency subscores (females tended to score higher on the tasks), as well as all FAT metrics (in our sample, females tended to have higher mean lesion load and HMOA and lower mean normalized volume). Thus, we included lesion volume and sex as covariates in our subsequent analyses. Because sex is not a typical covariate to account for, we additionally ran the analyses without the inclusion of sex as a covariate. The results changed minimally with the addition of sex as a covariate and are included in the Supplementary Materials (Supplementary Figure 3 and Supplementary Table 1).

3.4. Relationships between tract metrics and speech/language scores

3.4.1. Binomial GLMs between tract metrics and MSE scores

Binomial GLMs, adjusted for lesion volume and sex, were first performed to analyze the relationship between tract metrics and motor speech scores. All of the left hemisphere tract metrics (normalized volume, $\beta = 7.18$; HMOA, $\beta = 3.97$; lesion load, $\beta = -3.96$) showed a significant difference ($p < 0.05$) between patients with and without apraxia of speech, indicating that increased damage to the FAT (indexed by a lower NV & HMOA and higher lesion load) was associated with apraxia of speech. No such relationship was found for dysarthria, and right hemisphere tract metrics showed no significant relationship with either apraxia of speech or dysarthria scores.

Table 1
Participant tract metrics and language test scores. Values given as mean (±SD).

	Participant Metrics *(n = 32)*
Tract Metrics (LH)	
Volume (Norm.)	0.008 (±0.009)
HMOA	0.007 (±0.007)
Lesion Load	0.231 (±0 0.252)
Tract Metrics (RH)	
Volume (Norm.)	0.013 (±0.006)
HMOA	0.014 (±0.001)
Speech/Language Tasks	
MSE Apraxia	Score 0 (n = 14)*
MSE Dysarthria	Score 0 (n = 6)*
WAB AQ	82.60 (±17.42)
WAB Fluency	8.00 (±2.24)
WAB Info Content	8.688 (±1.86)
WAB Comprehension	8.825 (±1.31)
WAB Repetition	8.012 (±2.19)
WAB Naming	7.78 (±2.40)
WAB Category Fluency	10.52 (±6.19)
BNT	10.29 (±4.45)

* Score of 0 indicates presence of apraxia/dysarthria, score of 1 indicates absence of apraxia/dysarthria (as explained in the Methods).

3.4.2. Partial correlations for WAB & BNT

Among the language scores, WAB Comprehension, WAB Repetition, and WAB Naming scores were all significantly positively correlated with lesion load to the FAT ($p < 0.00625$). The positive association indicates that increased damage to the FAT is associated with better performance on these language tasks. A possible explanation for this unexpected pattern is explored in the Discussion and a scatterplot of residual data and raw data for WAB Fluency scores with lesion load to the FAT after controlling for lesion volume and sex is included in the Supplementary Materials (Supplementary Figure 4). WAB Repetition was significantly negatively correlated with the normalized volume of the FAT ($p < 0.00625$), again indicating that increased damage to the FAT is associated with better performance on this language task. All other left FAT metrics and all right hemisphere FAT metrics were not significantly correlated with any WAB language tasks. BNT was not significantly correlated with any FAT metrics in either the left or right hemispheres. Results of the partial correlations are shown in Fig. 3.

3.5. Modeling language results using tract metrics and lesion load to cortical areas

Based on the results above, we performed regressions to further investigate the predictive value of tract metrics on speech/language function beyond the contributions of cortical areas. Here, we were most interested in those speech/language scores where worse performance was associated with damage to the FAT. As a result, we only performed binomial logistic backwards stepwise regressions to model MSE Apraxia scores (where 0 indicates presence of AOS and 1 indicated absence of AOS) using FAT metrics (lesion load to the FAT, left hemisphere FAT normalized volume, and left hemisphere FAT HMOA), lesion load to cortical areas (IFG Opercularis, IFG Triangularis, vPCG, and SPGI), and sex as independent predictor variables. Lesion volume was not included as a covariate for these regressions due to multicollinearity, as it is highly correlated with lesion load to cortical areas. Separate regression models were run for each tract metric (normalized volume, HMOA, and lesion load) as these predictor variables were highly correlated (normalized volume with HMOA: $r = 0.82$, $p < 0.001$; HMOA with lesion load: $r = -0.84$, $p < 0.001$; lesion load with normalized volume: $r = -0.73$, $p < 0.001$).

With respect to normalized volume and HMOA, tract metrics and lesion loads to IFG triangularis and vPCG remained important predictors of apraxia of speech scores. However, when considering lesion load to the FAT, the tract metric became a less important predictor, and lesion load to SPGI and vPCG, in addition to sex, were the more important predictors. For these regressions, we saw that increased damage to the FAT, increased damage to the vPCG and SPGI cortical areas, and female sex predicted apraxia of speech. On the other hand, increased damage to the IFG triangularis cortical area predicted the absence of apraxia of speech. Regression results are reported in Table 2; only values for the significant predictors are shown as non-significant predictors were eliminated from the model.

3.6. Analysis of lateral vs medial FAT

We also performed an analysis to assess the functions of the lateral and medial segments of the FAT. As above, binomial GLMs or simple and partial correlations were run, adjusted for lesion volume and sex, between tract metrics and speech/language task performance as shown in Supplementary Figure 5. Similar to the results for the whole FAT, both

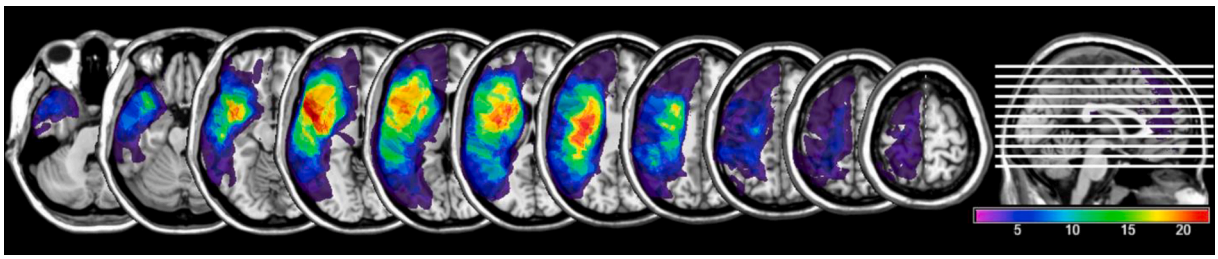

Fig. 2. Lesion overlay map ($n = 32$) demonstrating overlap of the participants' lesions, with brighter colors indicating greater number of participants having a lesion in each voxel (ranging from a minimum of one participant's lesion in a voxel and a maximum of 21).

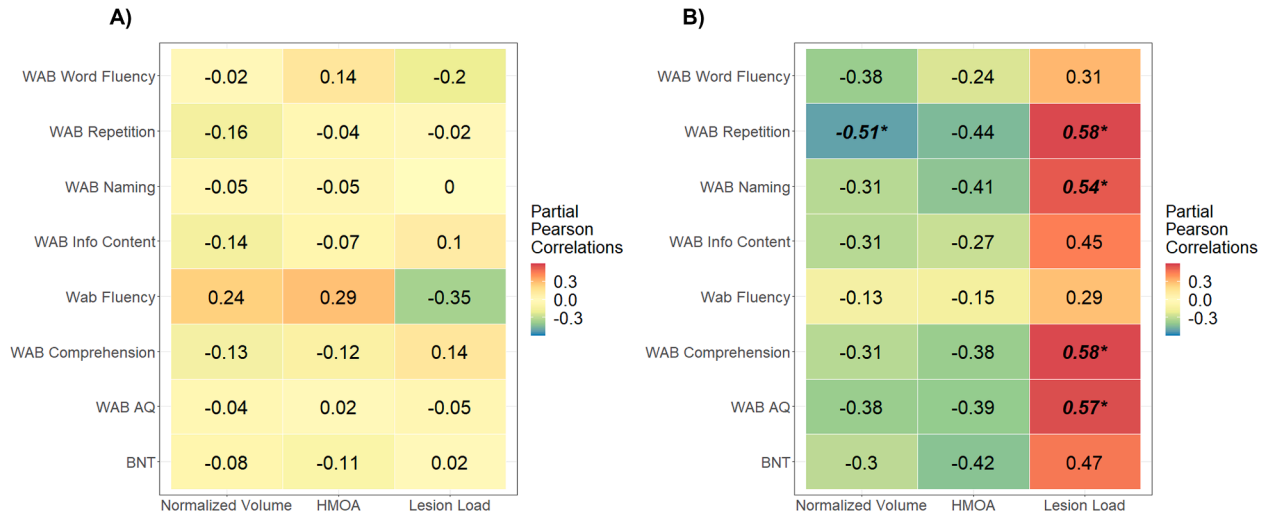

Fig. 3. Correlation matrices between language test scores and left hemisphere FAT metrics (normalized volume, HMOA, lesion load) showing A) simple correlations and B) partial correlations adjusted for lesion volume and sex. * - significant correlation at $p < 0.00625$ (Bonferroni-corrected).

Table 2
Backwards stepwise regressions for each individual tract metric of the left FAT predicting presence of apraxia of speech as indexed by the MSE Apraxia scores.

	B	SE	Deviance	df	p	Pseudo R^2
Normalized Volume			15.873	24	<0.001***	0.595
Sex	–	–				
LL to IFG Opercularis	–	–				
LL to IFG Triangularis	0.900	1.524				
LL to Ventral PCG	–	–				
LL to SPGI	–	–				
FAT LH Normalized Volume	392.261	146.542				
HMOA			17.408	23	<0.001***	0.555
Sex	–	–				
LL to IFG Opercularis	–	–				
LL to IFG Triangularis	1.889	1.912				
LL to Ventral PCG	−3.024	2.315				
LL to SPGI	–	–				
FAT LH HMOA	255.374	117.166				
Lesion Load			15.568	23	<0.001***	0.602
Sex	−2.944	2.084				
LL to IFG Opercularis	–	–				
LL to IFG Triangularis	–	–				
LL to Ventral PCG	−3.506	2.754				
LL to SPGI	−5.067	2.661				
FAT LH Lesion Load	–	–				

Notes. LL – lesion load.
– indicates that this variable was dropped out of the final model after stepwise regression.

medial segment metrics (normalized volume, $\beta = 6.49$; HMOA, $\beta = 3.45$) and lateral segment metrics (normalized volume, $\beta = 7.26$; HMOA, $\beta = 4.20$) in the left hemisphere distinguished between the groups with and without apraxia of speech ($p < 0.05$). No relationship was found between the FAT segments and dysarthria for any tract metrics. Among language metrics, WAB Repetition showed the strongest positive correlation with both segments.

We then performed backwards stepwise logistical regressions for each segment to determine the importance of FAT tract metrics for the individual segments in speech/language beyond the contributions of

cortical areas (Table 3). For normalized volume, the normalized volume of the lateral segment of the FAT and the lesion load to IFG triangularis were significant predictors of apraxia of speech. On the other hand, for HMOA, the results showed that the HMOA of the medial segment of the FAT, and the lesion loads to IFG triangularis, vPCG, and SPGI were all significant predictors of apraxia of speech. The directionality here was the same as above, indicating that increased damage to the FAT, vPCG, and SPGI predicted the presence of apraxia of speech while increased damage to IFG Triangularis predicted the absence of apraxia of speech. Again, female sex also predicted the presence of apraxia of speech when looking at the HMOA model. Of note, associations between the measures of tract integrity for the medial segment and the lateral segment were also investigated. The left hemisphere medial and lateral FAT HMOA were highly correlated ($r = 0.92, p < 0.001$). The left hemisphere medial and lateral FAT normalized volumes were also highly correlated ($r = 0.89, p < 0.001$).

4. Discussion

In this study, we assessed the specific role that the left FAT plays in speech and language abilities in a large, well-described cohort of PWA. As predicted, the loss of integrity of the FAT was associated with deficits in motor speech function. With regards to speech function, the FAT has previously been shown to be associated with stuttering (Kemerdere et al., 2016; Kronfeld-Duenias et al., 2016; Misaghi et al., 2018; Neef et al., 2018), speech arrest post-tumor resection (Fujii et al., 2015; Vassal et al., 2014), and speech fluency in individuals with resected glioma, post-stroke aphasia and primary progressive aphasia (Basilakos et al., 2014; Catani et al., 2013; Chernoff et al., 2018; Halai et al., 2017; Mandelli et al., 2014). Here, we found that damage to the FAT was associated with apraxia of speech, which, to our knowledge, is an association that has not previously been observed.

With respect to language function, we predicted that the FAT would be related to verbal fluency but not other language measures. Interestingly, we found that more FAT damage was associated with better language performance on WAB repetition, naming, comprehension subtests, and overall higher AQ once lesion volume and sex were accounted for. The shift in pattern seen with the addition of these covariates can be explained by the fact that larger lesions tend to affect additional language areas such as those found in the temporal lobe, thus affecting performance on language tasks. Once lesion volume was accounted for, the resulting finding likely reflects the fact that damage to the FAT is associated with more frontal lesions that are unlikely to involve other more posterior language areas of the brain and by themselves often do not lead to lasting language deficits (Gajardo-Vidal et al., 2021; Ivanova et al., 2021). At the same time, processes measured by the language tests used in the current study predominantly rely on the posterior language areas and tracts that are less likely to be affected by frontal lesions such as those that would affect the FAT. In other words, having a lesion affect the FAT often leads to core posterior language areas being spared, leading to less severe deficits in language processing.

Specifically, comprehension has been associated with temporal lobe regions and BA 46/47 (Dronkers et al., 2004; Turken & Dronkers, 2011), naming has been associated with the middle temporal gyrus (Baldo et al., 2013), and repetition has been associated with the superior temporal gyrus/sulcus and temporo-parietal cortex (Baldo et al., 2012; Miller et al., 2021). Thus, as predicted, damage to the FAT was not associated with decreased performance on repetition, naming, and comprehension tasks.

Contrary to prediction based on prior studies (Basilakos et al., 2014; Catani et al., 2013; Halai et al., 2017; Li et al., 2017; Mandelli et al., 2014), we did not observe a significant relationship between FAT damage and verbal fluency as measured by the WAB category fluency subtest. However, we would like to point out that, due to our Bonferroni correction, our significance threshold was more stringent compared to prior studies and that additionally we accounted for more covariates. The simple correlation between WAB category fluency and FAT metrics was positive for normalized volume and HMOA, and it was negative for lesion load (unlike other language scores). Specifically for lesion load, it was significant at $p = 0.05$, indicating that, at a conventional level of significance, we would have been able to detect an association between language fluency and FAT integrity. Additionally, this association is in the expected direction such that a higher lesion load to the FAT is associated with decreased performance on the category fluency test. Thus, it appears in line with previous findings demonstrating the association of the FAT with language fluency (Kinoshita et al., 2015; Li et al., 2017).

We ruled out the possibility that the observed association between FAT integrity and apraxia of speech was simply due to the lesions damaging the FAT also affecting adjacent cortical regions such as the IFG Opercularis, IFG Triangularis, vPCG, and SPGI by covarying for lesion load to these regions in stepwise regressions. Both normalized volume and HMOA of the FAT remained important predictors of apraxia of speech status even in the presence of lesion load to surrounding cortical areas. Lesion load to the FAT did not remain a significant predictor of apraxia status, with only lesion load to vPCG and SPGI remaining as significant predictors in this instance. However, it is possible that due to multicollinearity, lesion load to the FAT is eliminated from this regression model because of its close relationship with lesion load to surrounding cortical areas. Overall, these findings suggest

Table 3
Stepwise regressions predicting MSE Apraxia score from sex, cortical lesion load, and medial and lateral FAT metrics.

	B	SE	Deviance	df	p	Pseudo R^2
Normalized Volume			15.477	24	<0.001***	0.605
Sex	–	–				
LL to IFG Opercularis	–	–				
LL to IFG Triangularis	0.816	1.529				
LL to Ventral PCG	–	–				
LL to SPGI	–	–				
FAT LH Medial Normalized Volume	–	–				
FAT LH Lateral Normalized Volume	603.754	230.329				
HMOA			14.583	21	<0.001***	0.628
Sex	−1.685	1.171				
LL to IFG Opercularis	–	–				
LL to IFG Triangularis	0.961	1.701				
LL to Ventral PCG	−2.617	2.276				
LL to SPGI	−2.796	1.496				
FAT LH Medial HMOA	122.177	97.510				
FAT LH Lateral HMOA	–	–				

Notes. LL – lesion load.
– indicates that this variable was dropped out of the final model after stepwise regression.

that the integrity of the FAT, in addition to damage to local cortical areas, is an important predictor of apraxia of speech following stroke. Additionally, both normalized volume and HMOA more precisely reflect complete resection of the FAT unlike lesion load to the FAT (as the lesion load would not equal 100% even in cases when the FAT could not be reconstructed). Thus, it seems that the presence or absence of FAT fibers is more important for predicting apraxia status rather than the amount of fibers remaining or the amount of damage to those fibers.

The directions of the correlations between apraxia status and lesion load to cortical areas and FAT metrics also warrants further explanation. As expected, we found that increased damage to the FAT and increased lesion load to vPCG and SPGI were associated with presence of apraxia (Dronkers, 1996; Hillis et al., 2004; Ogar et al., 2005). However, we also found that increased lesion load to IFG Triangularis was associated with absence of apraxia of speech. Thus, it is likely that damage to the IFG Triangularis (and generally more anterior lesions) do not result in apraxic deficits but rather in other language and cognitive deficits such as semantic processing. In fact, Broca's area, which includes IFG Triangularis, may not display language deficits at all long-term after stroke (Gajardo-Vidal et al., 2021; Ochfeld et al., 2010). Interestingly, damage to the IFG Opercularis did not remain an important predictor in any of our models, pointing to the difference between damage to the cortex and damage to the underlying white matter tracts connecting cortical areas. This finding supports that in this case, the disconnection of the white matter via the FAT is a stronger factor for predicting apraxia of speech than the amount of damage to the cortical areas the tract connects. This finding is in line with multiple recent empirical studies and theoretical models that emphasize the importance of preserved structural connectivity between different language areas for successful processing (Bajada et al., 2015; Corbetta et al., 2015; Duffau et al., 2014; Ivanova et al., 2021; Kiran & Thompson, 2019; Tremblay & Dick, 2016; Turken & Dronkers, 2011).

We also analyzed the FAT with respect to its medial and lateral segments and found similar patterns to those with the overall FAT. Damage to both the medial and lateral segments were important predictors of apraxia of speech, and similar cortical regions demonstrated continued significance for predicting the presence of apraxia of speech with the same directional correlations as discussed for the overall FAT. Thus, these two FAT segments do not have differential functionality. It is important to recognize that, as mentioned in the results, the measures of FAT integrity are highly correlated between the medial and lateral segments. This high degree of correlation may have impacted our ability to detect a difference in function between the two segments because the lesions seemed to impact both segments of the FAT simultaneously. Thus, this may have made it challenging to tease apart their differential contributions to speech production. Additionally, we did not find diverging superior endpoints of the FAT segments in every participant in our cohort and thus what appears to be two segments is likely just an anatomical variant of the FAT in some individuals. Nevertheless, we found this anatomical dissociation to be of interest, and one that may warrant further exploration.

This study has several limitations that will need to be comprehensively addressed in future research. Larger sample sizes for future studies would allow for greater statistical power, greater generalizability of results, and further investigation of subgroups of participants based on different population characteristics. Additionally, it will be important to evaluate the role of the FAT in the acute stages of stroke and further explore its contribution to language and speech recovery post-stroke. A more detailed assessment of a wider range of speech production errors could be used in future studies to further determine the more specific aspects of speech production and speech praxis that are supported by the FAT.

In conclusion, we found that damage to the left FAT plays an important role in speech, specifically with regards to apraxia of speech. This finding adds to our knowledge about the neural correlates of apraxia of speech, which has previously been associated with damage to surrounding cortical areas such as the SPGI (Dronkers, 1996) and posterior IFG (Hillis et al., 2004). In addition to further characterizing anatomical variants of the FAT, this study underscores the important role of underlying white matter tracts such as the FAT in motor speech.

5. Ethics statement

This study was approved by the VA Northern California Health Care System. All participants provided their written informed consent to participate in this study.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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