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Contribution of White Matter Fiber Bundle Damage to Language Change After Surgery for Temporal Lobe Epilepsy

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Abstract:

Background and Objectives:
In medically refractory temporal lobe epilepsy (TLE), 30-50% of patients experience substantial language decline following resection in the language dominant hemisphere. Here, we investigate the contribution of white matter fiber bundle damage to language change at 3- and 12-months after surgery.

Methods:
We studied 127 patients who underwent TLE surgery from 2010–2019. Neuropsychological testing included picture naming, semantic, and phonemic verbal fluency, performed pre-operatively, 3- and 12-months post-operatively. Outcome was assessed using reliable change index (RCI; clinically significant decline) and change across timepoints (post- minus pre-operative scores).

Functional MRI was used to determine language lateralization. The arcuate (AF), inferior fronto-occipital (IFOF), inferior longitudinal, middle longitudinal (MLF), and uncinate fasciculi were mapped using diffusion MRI probabilistic tractography. Resection masks, drawn comparing co-registered pre- and post-operative T1 MRI scans, were used as exclusion regions on pre-operative tractography to estimate the percentage of pre-operative tracts transected in surgery. Chi-squared assessments evaluated the occurrence of RCI-determined language decline. Independent samples T-tests and MM-estimator robust regressions were used to assess the impact of clinical factors and fiber transection on RCI and change outcomes, respectively.

Results:
Language dominant and non-dominant resections were treated separately for picture naming, as post-operative outcomes were significantly different between these groups. In language dominant hemisphere resections, greater surgical damage to the AF and IFOF was related to RCI-decline at 3 months. Damage to the inferior frontal sub-fasciculus of the IFOF was related to change at 3 months. In language non-dominant hemisphere resections, increased MLF resection was associated with RCI-decline at 3 months, and damage to the anterior sub-fasciculus was related to change at 3 months.

Language dominant and non-dominant resections were treated as one cohort for semantic and phonemic fluency, as there were no significant differences in post-operative decline between these groups. Post-operative seizure freedom was associated with an absence of significant language decline 12 months after surgery for semantic fluency.

Discussion:
We demonstrate a relationship between fiber transection and naming decline after temporal lobe resection. Individualized surgical planning to spare white matter fiber bundles could help to preserve language function after surgery.

Introduction

Temporal lobe resection is an effective surgical treatment for medically refractory temporal lobe epilepsy (TLE). However, individuals undergoing language dominant resection have a 30-50% risk of significant post-operative decline in language-related functions.[1] Word finding difficulties can impact daily life.[2] Consequently, it is important to try to minimize the impact of temporal lobe surgery on language function.

Lateralization of visual and auditory naming fMRI activations in the ipsilateral temporal lobe predicts patients who will undergo a language decline.[3] However, surgically sparing fMRI-activated cortical regions does not avoid a naming decline in 50% of individuals.[4] Language function is dependent on a network involving multiple dispersed cortical regions.[5] Communication between these distant cortical regions is enabled by white matter fiber bundles, which are thus essential for language function.[6]

There have been several attempts at characterizing white matter involvement in post-operative language decline. White matter is anatomically organized in fiber bundles. Research using diffusion MRI (dMRI) found that pre-operative fractional anisotropy measures of the inferior longitudinal (ILF) and inferior fronto-occipital (IFOF) fasciculi correlated with post-operative picture and auditory naming decline, respectively.[7] Further research has extended this association by evaluating post-operative fractional anisotropy measures which correlate with post-operative language scores.[8] Whilst these studies correlate pre-operative and post-operative scores to pre-operative and post-operative diffusion metrics, they do not address the relationship between surgically-induced white matter damage and post-operative language decline.

Our aim in this study is to determine the correlations between surgical damage to language-related white matter tracts and the occurrence of post-operative language decline. We investigate several language-related fiber bundles that are at risk of damage during surgery: the arcuate (AF), uncinate (UF), ILF, middle longitudinal fasciculus (MLF), and IFOF.[9] The ultimate goal is to improve neurosurgical planning in each patient by avoiding these tracts, and minimize the risk of language function decline; analogous to the avoidance of surgical damage to the optic radiation for preventing visual field defects.[10]

Material and Methods

Participants

161 consecutive patients who underwent TLE surgery at the National Hospital of Neurology and Neurosurgery, London, United Kingdom between 2010 and 2019 were included. No patients underwent invasive language mapping and dMRI of language bundles was not considered when planning resections. 34 patients were excluded due to: previous neurosurgery (N=11), incomplete data (N=12), or bilateral language representation (N=11). All remaining patients had a pre-operative: T1-weighted structural MRI; dMRI; task-based language fMRI, and a post-operative T1-weighted MRI (obtained between 3- and 12-months post-operative).

Patients were stratified according to their language lateralization, derived from clinical reports of language fMRI and the quantitative fMRI lateralization index (LI)[11] based on a verbal fluency task.[12] Groups were defined by an LI>+0.2 (left-hemisphere dominant), -

0.2<LI<0.2 (bilateral), and LI<-0.2 (right-hemisphere dominant). Patients were dichotomized as having surgery on the language dominant (n=65) or non-dominant (n=62) hemisphere.

Standard Protocol Approvals, Registrations, and Patient Consents

This project was approved by London – Bloomsbury Research Ethics Committee (REC reference: 20/LO/0149; CAG number: 20/CAG/0013). Patient data were pseudo-anonymized, using a subject identification number which carried no information about the patient but could be referenced on a database with patient information if required. All patients had the opportunity to opt-out of research. This project did not carry any risk to participants and was retrospectively conducted on clinically acquired data.

Neuropsychology

Patients underwent the McKenna Graded Naming Test (referred to as picture naming),[13] phonemic verbal fluency (letter S, referred to as phonemic fluency), and categorical verbal fluency (category: animals, referred to as semantic fluency) assessments.[14] These were performed pre-operatively and post-operatively at 3- and 12-months. Patients with missing data on an assessment were excluded from analysis for that assessment only. For phonemic fluency, only the letter 'S' was performed as this was a presurgical screening assessment.

Change in neuropsychological performance was assessed using the reliable change index (RCI) and pre-operative and post-operative change. For picture naming, an RCI-decline of ≥4 was considered a clinically significant decline as per previous research.[3] For semantic and phonemic fluency, we use the test-retest RCI which were corrected for practice effects.[15] RCI was calculated as the standard deviation of score difference between assessment 1 and assessment 2 and multiplied by the 1.645 (Z_{CI} from the normal distribution). This equated to a decline of ≥9 for semantic fluency and ≥7 for phonemic fluency being a significant decline.[16] Language change was calculated as post-operative-pre-operative scores.

MRI Acquisition

Between 2009-2013 (N=80) patients were scanned on a 3T GE Signa Excite HDx. Single-shell dMRI data was acquired using a cardiac-triggered single-shot spin-echo planar imaging sequence[14]: 1.875×1.875×2.4mm resolution, gradient directions: 6 and 52 at *b*-values: 0 and 1200/mm^2, δ/Δ/TE=21/29/73ms, and a 3D T1-weighted sequence was acquired as described in.[17] Task-based verbal fluency and generation[14] gradient-echo planar T2*-weighted fMRI was acquired with 58 contiguous 2.5mm oblique axial slices, 96×96 matrix reconstructed to 128×128 for an in-plane resolution of 1.875×1.875mm (TE/TR=25/2500ms).

Between 2014-2019 (N=47) patients were scanned on a 3T GE Discovery MR750. A 3D T1-weighted sequence (MPRAGE) was acquired as in Vos et al.[18] and multi-shell dMRI (2mm isotropic resolution, gradient directions: 11, 8, 32, and 64 at *b*-values: 0, 300, 700, and 2500s/mm2; ∂/Δ=21.5/35.9ms, TE/TR=74.1/7600ms). Task-based verbal fluency and generation[14] gradient-echo planar T2*-weighted fMRI was acquired with 50 contiguous 2.4mm (0.1mm gap) slices with a 24cm field of view, 64×64 matrix with an in-plane voxel size of 3.75×3.75 mm (TE/TR=22/2500ms).

MRI Processing

Diffusion Processing

dMRI data was denoised,[19] Gibbs-unringed,[20] corrected for signal drift,[21] and distortion corrected using a synthesized b0 for diffusion distortion correction (Synb0-DisCo)[22] with FSL's topup.[23] Eddy currents and movement artifacts were corrected,[24] rotating the b-vectors.[25] Additionally, bias-field correction was performed in MRtrix3.[22] Response functions for cerebrospinal fluid, white and grey matter were estimated using Single-Shell 3-Tissue[27] and Multi-Shell 3-Tissue[28] CSD in MRtrix3.[22]

fMRI Processing

Hemispheric language lateralization was calculated using the bootstrap method of the lateralization index toolbox implemented in SPM8[29] on verbal fluency spmT maps, using the WFU PickAtlas' anatomical masks of the middle and inferior frontal gyrus (including the pars triangularis, orbitalis, opercularis).[30] LI values were calculated: [LI=(L–R)/(L+R)].

Resection Mask

Resection masks were drawn based on previous techniques.[17] Post-operative T1-weighted MRI were affinely registered to pre-operative T1-weighted MRI. Resection masks were then manually drawn in MRtrix3 by overlaying the post-operative T1-weighted MRI on the pre-operative T1-weighted MRI starting at the most anterior coronal slice of the temporal lobe, then proceeding posteriorly every three slices. Coronal slices were then joined by drawing in every sagittal slice. Masks were saved in pre-operative T1-weighted space. Resection mask reliability and validity were assed via inter-rater reliability between two raters. Impact of delineation accuracy was assessed using dilated resection masks (eTables 1 and 2 in eAppendix 1).

Anatomically Targeted–Automated Tractography

Details on tractography reconstruction can be seen in eAppendix 2 and cortical terminations in eTable 3 (eAppendix 2).

Change in fiber bundles from pre-operative to estimated post-operative was calculated as the percentage difference using the following formula: ((post-operative−pre-operative)÷pre-operative)×100.

Statistical Analysis

Statistical analysis was performed to assess the relationship between RCI-decline and the following clinical features: fMRI LI, age of epilepsy onset, epilepsy duration at time of surgery, seizure freedom at 12 months (ILAE outcome 1), and resection volume. Additionally, the relationship between RCI-decline and the following fiber bundles were analyzed: AF, IFOF, ILF, MLF, and UF.

We used a chi-squared test to assess whether there was a difference in RCI-decline between patients with language dominant and language non-dominant resections.

To assess feature differences between those with RCI-decline and non-decline in those with language dominant and non-dominant resections, we used independent samples t-test with

false discovery rate (FDR) to control for multiple comparisons. This was used to identify features that could have a linear relationship to language change.

We used a robust linear regression to determine if there was sub-fascicle specialization within the fiber bundles significant at the RCI t-test analysis and show if there was a linear relationship or a cut-off point at which performance drops. We used language change (post-operative-pre-operative scores) as the dependent variable. We picked the MM-estimator[31] regression algorithm for its ability in controlling for outliers, performing similarly to ordinary least squares on uncontaminated data.[32] Variables entered into the model as fixed effects were based on features that showed significance in the 3- or 12-month independent samples T-test analysis (section 3.b). Fiber bundles significant in the T-test analysis were split into their respective sub-fasciculi. Confounding effects (fMRI LI and resection volume) were included in all models. Features were normalized before inclusion in the model by shifting the mean to 0 and scaling to have a standard deviation of 1. All features were entered into the regression and the robust final prediction error (RFPE)[31] was calculated. Features were removed one-by-one to minimize the RFPE (indicating a better model). To assess the impact of outlier handling in the robust estimator, we repeated these regressions using a second robust regression method, the talwar algorithm, which also has demonstrated performance on our sample size (eAppendix 3).

Sensitivity Analysis

To assess whether results were dependent on a combination of more limited temporal lesionectomies and anterior temporal lobe resection (ATLR) we performed the same analysis on a sub-cohort of ATLR patients. A full comparison of sub-groups can be seen in eAppendix 4 (eTable4) and visualized in eFigures 1–2.

To assess if the results of this paper could be modelled across both 3- and 12-month decline, we applied the final models of this paper in a generalized mixed effect model. The results of this analysis can be seen in eAppendix 5, eTable 5 pitfalls are discussed and visualized in eFigures 3–4.

Data Availability

Anonymized data that these results were based on and were not published within this article and will be made available on request from any qualified investigator.

Results

A summary of significant features to language assessments is given in Table 1. Only significant findings are reported, detailed statistics of non-significant findings are shown in eAppendix 6 eTable 6-11.

1. Descriptive Statistics

Demographic information can be seen in Table 2.

The 65 language dominant hemisphere patients (33 female) comprised: 61 with left-language lateralization and left-resection; 4 with right-language lateralization and right-resection. 54 patients underwent ATLR and 11 underwent a more limited lesionectomy. Pathology in this group included: hippocampal sclerosis (HS; N=36), cavernoma (CAV; N=6), dysembryoplastic neuroepithelial tumor (DNT; N=10), dual pathology (N=6), and other (N=7). There were several patients with missing scores for picture naming at 3 months (N=8), 12 months (N=20), semantic fluency at 3 months (N=7), and 12 months (N=19), phonemic fluency at 3 months (N=7) and 12 months (N=19). These patients were excluded from these assessments only.

The 62 language non-dominant hemisphere patients (38 female) comprised: 57 with left-language lateralization and right-resection; 5 with right-language lateralization and left-resection. 57 patients underwent ATLR, and 5 underwent a more limited lesionectomy. Pathology for this group included: HS (N=32), CAV (N=4), DNT, (N=7), dual pathology (N=5), and other (N=12). There were several patients with missing scores for picture naming at 3 months (N=8), 12 months (N=17), semantic fluency at 3 months (N=4), and 12 months (N=15), phonemic fluency at 3 months (N=4) and 12 months (N=15). These patients were excluded from these assessments only.

2. Language Performance

2.a. Hemispheric Dominance and Performance

Pre-operative and post-operative language scores are summarized in Table 3. Cross-sectional analysis was performed to identify if there were significant differences in scores between language dominant and non-dominant groups. A chi-squared test of independence was used to assess group differences of those that did have RCI-decline at 3- and 12-months between language dominant and non-dominant patients.

For picture naming, patients with language dominant resections had lower scores across all three timepoints compared to language non-dominant resections (Table 3). Furthermore, a chi-squared assessment showed significant differences between the number of patients that had declined at 3 months on language dominant (19/57, 33.3% of patients) compared to non-dominant (5/54, 9.3%) resection ($\chi(1)=9.483$, $p=0.002$, Odds=4.900, 95% Confidence Interval (CI95):1.677:14.139), and at 12 months with significantly higher language dominant (12/45, 26.7%) than non-dominant (2/45, 4.5%) resections causing RCI-decline ($\chi(1)=8.459$, $p=0.004$, Odds=7.818, 95CI:1.636:37.360). This demonstrates there were clinically significant different outcomes between language dominant and non-dominant hemisphere resections. As such, our remaining analysis will use separate dominant and non-dominant groups to identify clinically significant differences per group.

For semantic fluency, surgery in language dominant patients was associated with a drop in performance at 3 months, and slight improvement at 12 months but not reaching pre-operative levels (Table 3). In contrast, semantic fluency scores were higher following surgery to non-dominant temporal lobes at both 3- and 12-months. A chi-squared test, however, of those that had RCI-decline showed that there were no significant differences in the language dominant (6/58, 10.3%) compared to non-dominant (3/58, 5.2%) at 3- and 12-months

(language dominant=5/46, 10.9% vs. non-dominant=2/47, 4.3%). This suggests there are no clinically significant differences in semantic fluency outcome between language dominant and non-dominant resections. Our remaining analysis will combine dominant and non-dominant resections in one group.

For phonemic fluency, language non-dominant groups had higher pre-operative scores than the dominant group (Table 3). However, a chi-squared assessment of those that had RCI-decline showed that there were no significant differences between the language dominant (8/58, 13.8% of patients) and non-dominant resections (3/58, 5.2% of patients) at 3- and 12-months (language dominant=6/46, 13% vs. non-dominant=5/47, 10.6% of patients). Our remaining analysis will combine dominant and non-dominant resections in one group.

3. ***Differences in resections and change in language***

3.a. Scanner Effect on Features
An independent samples t-test showed there was a significant difference between scanner type and AF resection (p=0.001, d=0.587, 95CI:0.225:0.947). Consequently, the AF was harmonized across scanners.[33]

3.b. Dominant vs. Non-dominant Hemisphere
To assess feature differences between language dominant and non-dominant patients we used an independent samples t-test at an alpha-level of 0.05 with FDR correction.

Resection volume were 29.0% greater on the non-dominant (Mean=34.8ml±Standard Deviation=9.8ml) than dominant hemisphere resections (27.0ml±9.8ml): p<0.001, *Cohen's d (d)*=0.784, CI95:0.421:1.144. IFOF resection was 51.0% greater on the non-dominant (46.8%±31.8%) than dominant hemisphere resections (31.0%±33.5%): p=0.007, d=0.484, CI95:0.130:0.836. ILF resection was 39.9% greater on the non-dominant (82.6%±16.3%) than dominant hemisphere resection (59.0%±28.7%): p<0.001, d=1.004, CI95:-0.633:1.372. MLF resection was 338.7% greater on the dominant (28.2%±13.5%) than non-dominant hemisphere resections (8.3%±15.3%): p<0.001, d=1.375, CI95:0.985:1.760.

3.c. RCI Group Level Feature Differences
To assess feature differences between those with and without RCI-decline we used an independent sample t-test at an alpha-level of 0.05 with FDR correction. For picture naming on the language dominant hemisphere at 3 months: epilepsy duration was 30% greater for those with RCI-decline (27.0y±15.9y) than those without RCI-decline (18.9y±11.9y): p=0.033, d=-0.613, CI95:-1.173:-0.048. Resection volume was 28.5% greater for those with (31.9ml±9.7ml) than those without RCI-decline (24.8ml±10.3ml): p=0.016, d=-0.697, CI95:-1.260:-0.128. AF resection as 218.5% greater for those with (5.9%±7.7%) than those without RCI-decline (2.7%±3.6%): p=0.032, d=-0.619, CI95:-1.179:-0.053. IFOF resection was 91.9% greater for those with (44.7%±38.3%) than those without RCI-decline (23.3%±27.9%): p=0.019, d=-0.676, CI95:-1.238:-0.109. There were no significant differences at 12 months.

For picture naming on the language non-dominant hemisphere at 3 months: MLF resection was 486.2% greater for those with RCI-decline (31.2%±39.8%) than those without RCI-decline (5.3%±6.9%): p<0.001, d=-2.009, CI95:-2.998:-1.003. There were no significant differences at 12 months.

For semantic fluency at 3 months and 12 months there were no significant differences.

For phonemic fluency at 3 months post-operatively: epilepsy duration at operation was 42.5% greater for those with RCI-decline (29.6y±14.4y) than those without RCI-decline (20.8y±13.3y): p=0.040, d=-0.658, CI95: -1.283:-0.029. This same relationship was observed at 12 months, where epilepsy duration at operation was 46.9% greater for those with RCI-decline (28.6y±15.11y) than those without RCI-decline (19.5y±13.2y): p=0.037, d=-0.679, CI95:-1.314:-0.040.

3.d. Seizure Freedom and Language Outcome

To assess if there was a significant difference in those with and those without RCI-decline and one-year seizure freedom, we used a chi-squared assessment.

For picture naming there were no significant differences at 3 or 12 months on the language dominant or non-dominant hemisphere.

For semantic fluency, there were no significant differences at 3 months. At 12 months, there was a significant difference between those who were seizure free without RCI-decline (58.1%) compared to with (14.3%): p=0.025, Odds=0.120, CI95:0.01:1.040.

For phonemic fluency, there were no significant differences at 3 or 12 months.

3.e. Seizure Freedom and Resection Volume

An independent samples t-test for both language dominant and non-dominant resections, showed there was no significant difference between resection volume and seizure-freedom at one-year.

4. Correlation of Sub-fascicles and 3- or 12-Month Neuropsychology Change

To assess if there was a linear relationship between features and neuropsychology score change from pre-operative to 3- or 12-months post-operatively (post-operative–pre-operative score) we used a robust least squares regression. Features assessed were based on significant group differences between those with and without RCI-decline (section 3.b). Fiber bundles were segmented into sub-fasciculi according to previous research. Confounds (fMRI LI and resection volume) were added to each model.

4.a. Picture Naming

4.a.1. Language Dominant Hemisphere

The IFOF was segmented into three[34] and the AF into two sub-fasciculi.[35] Resection of the AF's ventral sub-fasciculus was significantly different between scanner types (p=0.006, d=0.724, 95CI 0.210:1.234) and was harmonized[33] to remove scanner effect.

For picture naming at 3 months, the best model (Table 4; RFPE=0.1895, $\chi 2(1,39)=4.906$, p=0.027, adjusted R^2=0.137) included: confounds (fMRI LI (p=0.392), total resection volume (p=0.650)) and surgical damage to the inferior frontal sub-fasciculus of the IFOF (IFG-IFOF; p=0.033, β=-1.417, CI95:0.163:2.671) (Figure 1). This translates to IFG-IFOF damage resulting in an increased risk of picture naming decline, explaining 13.7% of decline. This model outperformed a confounds-only model (see Table 4 for full details). An example of a patient with the IFOF spared is shown in Figure 3A.

The best model was marginally different in the typical ATLR sub-group of patients, with the IFG-IFOF maintaining significance (see eAppendix 5, eTable 10).

4.a.2. *Language Non-dominant Hemisphere*

The MLF was segmented into two sub-fasciculi.[36] For picture naming at 3 months, the best model (Table 4; RFPE=0.138, $\chi 2(1,49)=6.601$, $p=0.010$, adjusted $R^2=0.073$) included: confounds (fMRI LI ($p=0.650$), total resection volume ($p=0.707$)) and surgical damage to the anterior sub-fasciculus of the MLF (MLFa; $p=0.013$, $\beta=-0.351$, CI95:-0.618:-0.083) (Figure 2). Practically, this translates to MLFa damage resulting in an increased risk of picture naming decline, explaining 7.3% of decline. This model outperformed a confounds-only model (see Table 4 for full details). An example of a patient with the MLF spared is shown in Figure 3B.

Analysis of the typical ATLR sub-group of patients included same features in the best model but no overall significance (see eAppendix 5, eTable 10).

4.b. Semantic and Phonemic fluency

There were no significant pre-operative or post-operative features associated with semantic or phonemic fluency outcome.

Discussion

Previous research has implicated white matter fiber bundles in pre-operative or post-operative language function in TLE surgery,[37] albeit with limited translational capability for surgical targeting to prevent language decline following surgery. Using resection masks and pre-operative tractography, we document a direct relationship between picture naming and fiber bundles transection which is clinically implementable for future surgery.

Typically, patients are split into language dominant and non-dominant when assessing the risk of language decline. We demonstrated significantly different outcomes for picture naming between these groups, supporting previous literature.[38] However, there was no significant difference in semantic and phonemic fluency outcome between language dominant and non-dominant resections. Thus analyses of picture naming outcome split patients into language dominant and non-dominant resections, whereas both groups were combined for semantic and phonemic fluency analyses.

Picture Naming – Language Dominant Resection

At 3 months we showed that there is a significant difference between IFOF resection, AF resection, epilepsy age of onset, and resection volume between those with and without RCI-decline. These were not significant at 12 months. Modeling picture naming change as a linear combination of these features, the IFG-IFOF was significantly correlated with outcome, with greater damage being associated with worse language outcome. In the ATLR-only sub-group, we demonstrated the same IFOF sub-fasciculus correlated with language change (eAppendix 1, eTable 1).

Our findings support that preservation of the IFOF is related to post-operative picture naming function.[7] The IFOF has been implicated in picture naming ability, although there is no consensus on the exact function of IFOF.[5] Solely the IFG-IFOF was correlated with naming

decline. This suggests a functional specialization within the IFOF, which may account for inconsistencies in the literature that measured the bundle as an unspecific whole.

The AF interconnects the superior, middle, and inferior temporal gyri to the frontal lobe.[5] The middle and inferior temporal gyri are both involved in semantic storage.[5] Our results highlight the role of the AF in relaying semantic information to the frontal lobe for picture naming ability.

Resection volume is a combination of white and grey matter resection. This suggests that both grey matter and white matter resection may play a role in picture naming decline at 3 months – reinforcing picture naming as a multifaceted function involving dispersed cortical regions requiring structural connections.[6]

Earlier onset of TLE is associated with atypical functional language representation.[39] Hence, there could be efficient functional reorganization (i.e., away from the epileptogenic zone) with earlier onset. Future research confirming this would open the possibility of targeted therapies to promote reorganization away from the anterior temporal lobe prior to surgery.[40]

Picture Naming – Language Non-dominant Resection

At 3 months, there were significant group differences in MLF resection between those with and without RCI-decline. Modeling picture naming change as a linear combination of predictive features, resection of MLFa connections were significantly correlated with significant decline. In the ATLR-only sub-group, this model remained the best but lost overall significance (eAppendix 1, eTable 1).

The MLF terminations (superior temporal gyrus and temporal pole to the parietal lobe) are important for language function.[5] We find evidence for a role of the MLF in picture naming function. MLFa extensions are implicated in retrieving auditory information consolidated in the temporal lobe.[41] There is evidence in the literature that the superior temporal gyrus in TLE is involved in semantic function.[5] Future research should try and delineate if any fMRI-activated regions in TLE overlap with the MLF in picture naming to confirm our finding.

Semantic Fluency – Language Dominant and Non-dominant Resections

Continued seizures 12 months after dominant and non-dominant resections were associated with semantic fluency impairment. We infer that ongoing seizure activity is related to the continued dysfunction of functional networks.

Phonemic Fluency – Language Dominant and Non-dominant Resections

Longer duration of epilepsy was significantly related to an RCI-decline of phonemic fluency at 3 months.

Epilepsy duration is an indirect measure of cumulative seizure burden. Previous research has shown high performance on phonemic fluency is contingent on a highly-connected network of dispersed cortical regions across the frontal and parietal lobes.[43] The strength of connectivity in the frontal and parietal regions could be negatively impacted by long-term seizure burden,[44] and thus lead to poor performance post-operatively. Future research should aim to clarify whether clinical factors directly impacts upon frontal lobe connectivity.

Clinical Impact

The language network is complex and widespread, recovery of healthy function after surgery can occur with grey and white matter plasticity, facilitating functional reorganization.[45] Surgical damage to both grey and white matter has been associated with post-operative naming decline, but this has not been translated into clinical practice.[37] Here we present findings that can be utilized in clinical settings to mitigate some of the risks of temporal lobe surgery to language function.

Typically, a standard ATLR in the language dominant temporal lobes involves complete dissection of the temporal UF and anterior-temporal extensions of AF, MLF, and ILF, with resection of the anterior 2-3 cm of the superior temporal gyrus, the anterior hippocampus and amygdala. Middle and inferior temporal gyri resection extends 4-5 cm posterior to the pole, aiming to spare the posterior temporal cortex, including the fusiform gyrus. The IFOF runs along the boundary of the resection margin, which explains the high variability in the extent of resection. Adapting dominant temporal lobe surgery to avoid IFOF while reducing the lateral neocortical resection may mitigate post-operative picture naming impairment. In the non-dominant temporal lobe, greater proportions of superior temporal gyrus and lateral neocortex are typically resected. Our results suggest that preserving the MLFa will mitigate adverse effects on picture naming function.

Sparing the IFOF and MLF during surgery to help preserve some language function could be possible with smaller resections, as we showed resection size was not related to post-operative seizure freedom. However, there was individual variation in white matter fiber bundles anatomy. As such, to increase the specificity of surgery in preserving language, an intra-operative display overlaying the tractographic representations could be used. We have established this technique to be beneficial to preserving vision in the case of the optic radiation.[10] We aim to implement this technique by displaying the IFOF, MLF, and the optic radiation[10] for optimal neurocognitive outcomes.

Research Evaluation

All patients included in this study had surgery performed by the same two surgeons. This had the benefit of ensuring there was a consistent surgical approach for all cases; however, replication studies may improve the generalizability of our findings to other centers.

Several steps were taken to ensure the accuracy of our methods. For tractography: 1) a region-of-interest (ROI)-to-ROI seeding method was used which has been shown to be highly accurate.[46] 2) Probabilistic tractography was chosen for its high sensitivity. 3) Tractography was performed in both directions, flipping ROIs to ensure that there was no bias in the direction of tractography and resulting in twice as many streamlines in the main stem of the sub-fasciculus. 4) An automatic pruning method was used to remove spurious tracts, ensuring the main component of the fasciculus remained. These steps increased the replicability of our results.

The use of manually-drawn resection masks to estimate post-operative tractography has the benefit of the rater being able to visually estimate for brain-shift but may introduce human error and image registration issues. Additional analyses were performed to investigate these issues and showed minimal impact (eAppendix 2). Furthermore, some sub-fasciculi were not reconstructed in some patients, which resulted in reduced cohort sizes for the sub-fasciculi evaluations. Although this could be rectified by tracking each sub-fasciculus independently, this introduces new biases.

We used the percentage-change between pre-operative and post-operative streamline count to yield a proxy of resection damage to tracts, and we did not account for microstructural diffusion metrics. Pre-operative microstructural measures within tracts have been shown to correlate with performance.[8] Variability shown in the relationship between resection damage and language decline (Figures 1,2) in these patients could be due to a pre-existing dysfunction of this fiber bundle. Alternatively, this could be related to plasticity potential or successful functional reorganization. Future work should explore if any of these factors further improve the model's accuracy in helping to prevent language decline from surgical white matter damage, and to balance this with potential effects on the chance of post-operative seizure freedom.

Conclusion

Our results suggest that white matter fiber bundle damage correlates with adverse effects on language function, demonstrating that greater damage to the IFG-IFOF in language-dominant resections and MLFa damage in non-dominant resection are associated with poorer post-operative picture naming performance. We hope this work will lead to reducing language decline following temporal lobe resection by planning and navigating surgery to avoid these fiber bundles. In parallel, it is important to evaluate whether there is any impact on seizure outcome.

References

1. Sherman EM, Wiebe S, Fay- McClymont TB, et al. Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. Epilepsia. 2011;52:857–869.

2. Zhao F, Kang H, You Li, Rastogi P, Venkatesh D, Chandra M. Neuropsychological deficits in temporal lobe epilepsy: a comprehensive review. Annals of Indian Academy of Neurology. Wolters Kluwer–Medknow Publications; 2014;17:374.

3. Trimmel K, van Graan LA, Gonzálvez GG, et al. Naming fMRI predicts the effect of temporal lobe resection on language decline. Annals of clinical and translational neurology. Wiley Online Library; 2019;6:2186–2196.

4. Davies KG, Risse GL, Gates JR. Naming ability after tailored left temporal resection with extraoperative language mapping: increased risk of decline with later epilepsy onset age. Epilepsy & Behavior. Elsevier; 2005;7:273–278.

5. Binding LP, Dasgupta D, Giampiccolo D, Duncan JS, Vos SB. Structure and function of language networks in temporal lobe epilepsy. Epilepsia. Wiley Online Library; 2022;63:1025–1040.

6. Trimmel K, Vos SB, Caciagli L, et al. Decoupling of functional and structural language networks in temporal lobe epilepsy. Epilepsia. Wiley Online Library; Epub 2021.

7. Kaestner E, Stasenko A, Ben-Haim S, Shih J, Paul BM, McDonald CR. The importance of basal-temporal white matter to pre-and post-surgical naming ability in temporal lobe epilepsy. NeuroImage: Clinical. Elsevier; 2022;34:102963.

8. Pustina D, Doucet G, Evans J, et al. Distinct types of white matter changes are observed after anterior temporal lobectomy in epilepsy. PloS one. Public Library of Science; 2014;9:e104211.

9. Mancini M, Vos SB, Vakharia VN, et al. Automated fiber tract reconstruction for surgery planning: Extensive validation in language-related white matter tracts. NeuroImage: Clinical. Elsevier; 2019;23:101883.

10. Winston GP, Daga P, White MJ, et al. Preventing visual field deficits from neurosurgery. Neurology. AAN Enterprises; 2014;83:604–611.

11. Adcock JE, Wise RG, Oxbury J, Oxbury S, Matthews P. Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. Neuroimage. Elsevier; 2003;18:423–438.

12. Yuan W, Szaflarski JP, Schmithorst VJ, et al. fMRI shows atypical language lateralization in pediatric epilepsy patients. Epilepsia. Wiley Online Library; 2006;47:593–600.

13. Warrington EK. The graded naming test: a restandardisation. Neuropsychological Rehabilitation. Taylor & Francis; 1997;7:143–146.

14. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Archives of clinical neuropsychology. Elsevier; 1999;14:167–177.

15. Thompson P, Baxendale S, McEvoy A, Duncan J. Cognitive outcomes of temporal lobe epilepsy surgery in older patients. Seizure. Elsevier; 2015;29:41–45.

16. Bird CM, Papadopoulou K, Ricciardelli P, Rossor MN, Cipolotti L. Monitoring cognitive changes: Psychometric properties of six cognitive tests. British Journal of Clinical Psychology. Wiley Online Library; 2004;43:197–210.

17. Taylor PN, Sinha N, Wang Y, et al. The impact of epilepsy surgery on the structural connectome and its relation to outcome. NeuroImage: Clinical. 2018;18:202–214.

18. Vos SB, Winston GP, Goodkin O, et al. Hippocampal profiling: Localized magnetic resonance imaging volumetry and T2 relaxometry for hippocampal sclerosis. Epilepsia. Wiley Online Library; 2020;61:297–309.

19. Veraart J, Novikov DS, Christiaens D, Ades-aron B, Sijbers J, Fieremans E. Denoising of diffusion MRI using random matrix theory. NeuroImage. 2016;142:394–406.

20. Kellner E, Dhital B, Kiselev VG, Reisert M. Gibbs-ringing artifact removal based on local subvoxel-shifts. Magnetic resonance in medicine. Wiley Online Library; 2016;76:1574–1581.

21. Vos SB, Tax CM, Luijten PR, Ourselin S, Leemans A, Froeling M. The importance of correcting for signal drift in diffusion MRI. Magnetic resonance in medicine. Wiley Online Library; 2017;77:285–299.

22. Schilling KG, Blaber J, Huo Y, et al. Synthesized b0 for diffusion distortion correction (Synb0-DisCo). Magnetic resonance imaging. Elsevier; 2019;64:62–70.

23. Andersson JL, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage. Elsevier; 2003;20:870–888.

24. Andersson JL, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage. Elsevier; 2016;125:1063–1078.

25. Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine. Wiley Online Library; 2009;61:1336–1349.

26. Tournier J-D, Smith R, Raffelt D, et al. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. NeuroImage. Elsevier; 2019;202:116137.

27. Dhollander T, Connelly A. A novel iterative approach to reap the benefits of multi-tissue CSD from just single-shell (+ b= 0) diffusion MRI data. Proc ISMRM. 2016. p. 3010.

28. Dhollander T, Mito R, Raffelt D, Connelly A. Improved white matter response function estimation for 3-tissue constrained spherical deconvolution. Proc Intl Soc Mag Reson Med. 2019.

29. Wilke M, Lidzba K. LI-tool: a new toolbox to assess lateralization in functional MR-data. Journal of neuroscience methods. Elsevier; 2007;163:128–136.

30. Szaflarski JP, Gloss D, Binder JR, et al. Practice guideline summary: Use of fMRI in the presurgical evaluation of patients with epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. AAN Enterprises; 2017;88:395–402.

31. Maronna RA, Martin RD, Yohai VJ, Salibián-Barrera M. Robust statistics: theory and methods (with R). John Wiley & Sons; 2019.

32. Finger R. Revisiting the evaluation of robust regression techniques for crop yield data detrending. American Journal of Agricultural Economics. Wiley Online Library; 2010;92:205–211.

33. Fortin J-P, Parker D, Tunç B, et al. Harmonization of multi-site diffusion tensor imaging data. Neuroimage. Elsevier; 2017;161:149–170.

34. Panesar SS, Yeh F-C, Deibert CP, et al. A diffusion spectrum imaging-based tractographic study into the anatomical subdivision and cortical connectivity of the ventral external capsule: uncinate and inferior fronto-occipital fascicles. Neuroradiology. Springer; 2017;59:971–987.

35. Fernández-Miranda JC, Wang Y, Pathak S, Stefaneau L, Verstynen T, Yeh F-C. Asymmetry, connectivity, and segmentation of the arcuate fascicle in the human brain. Brain Structure and Function. Springer; 2015;220:1665–1680.

36. Latini F, Trevisi G, Fahlström M, et al. New insights into the anatomy, connectivity and clinical implications of the middle longitudinal fasciculus. Frontiers in neuroanatomy. Frontiers; 2020;14:106.

37. Powell HR, Parker GJ, Alexander DC, et al. Imaging language pathways predicts postoperative naming deficits. Journal of Neurology, Neurosurgery & Psychiatry. BMJ Publishing Group Ltd; 2008;79:327–330.

38. Ives-Deliperi VL, Butler JT. Naming outcomes of anterior temporal lobectomy in epilepsy patients: a systematic review of the literature. Epilepsy & Behavior. Elsevier; 2012;24:194–198.

39. Dijkstra KK, Ferrier CH. Patterns and predictors of atypical language representation in epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 2013;84:379–385.

40. Binney RJ, Ralph MAL. Using a combination of fMRI and anterior temporal lobe rTMS to measure intrinsic and induced activation changes across the semantic cognition network. Neuropsychologia. Elsevier; 2015;76:170–181.

41. Wang Y, Fernández-Miranda JC, Verstynen T, Pathak S, Schneider W, Yeh F-C. Rethinking the role of the middle longitudinal fascicle in language and auditory pathways. Cerebral cortex. Oxford University Press; 2013;23:2347–2356.

42. Jo HJ, Kenney-Jung DL, Balzekas I, et al. Relationship between seizure frequency and functional abnormalities in limbic network of medial temporal lobe epilepsy. Frontiers in Neurology. Frontiers Media SA; 2019;10:488.

43. Gonzalez-Burgos L, Pereira JB, Mohanty R, Barroso J, Westman E, Ferreira D. Cortical networks underpinning compensation of verbal fluency in normal aging. Cerebral Cortex. Oxford University Press; 2021;31:3832–3845.

44. Nagy SA, Horváth R, Perlaki G, et al. Age at onset and seizure frequency affect white matter diffusion coefficient in patients with mesial temporal lobe epilepsy. Epilepsy & Behavior. Elsevier; 2016;61:14–20.

45. Osipowicz K, Sperling MR, Sharan AD, Tracy JI. Functional MRI, resting state fMRI, and DTI for predicting verbal fluency outcome following resective surgery for temporal lobe epilepsy. Journal of neurosurgery. American Association of Neurological Surgeons; 2016;124:929–937.

46. Schilling KG, Petit L, Rheault F, et al. Brain connections derived from diffusion MRI tractography can be highly anatomically accurate—if we know where white matter pathways start, where they end, and where they do not go. Brain Structure and Function. Springer; 2020;225:2387–2402.

Tables

Table 1. Significant features to language assessments and at which timepoint.

	Assessment	3 Months	12 Months
Language Dominant Resections	Picture Naming	Epilepsy duration[a]* Resection Volume[a]* AF[a]* IFOF[a]* IFG-IFOF[c]*	N/A
Language Non-dominant Resections	Picture Naming	MLF[a]*** MLFa [c]*	N/A
Language Dominant and Non-dominant Resections	Semantic Fluency Phonetic Fluency	N/A Epilepsy duration[a]*	Seizure freedom[b]* Epilepsy duration[a]*

**** p < 0.001, ** p < 0.01, * p < 0.05 indicates significant level across varying tests: independent samples t-test, chi-squared test, and robust linear regression.*
Abbreviations: AF: arcuate fasciculus; IFOF: inferior fronto-occipital fasciculus; MLF: middle longitudinal fasciculus; MLFa; anterior sub-fasciculus of the MLF; IFG-IFOF inferior frontal sub-fasciculus of the IFOF; N/A: not applicable.

[a] Independent samples T-test

[b] Chi-squared test

[c] Robust linear regression

Table 2. Baseline demographic information of our cohorts. Values are given as mean (standard deviation).

	Resections in language Dominant Hemisphere	*Resections in language Non-dominant Hemisphere*
fMRI LI	*0.75 (0.19)*	*0.69 (0.25)*
Age of epilepsy onset (yr)	*16.43 (12)*	*17.76 (12.11)*
Epilepsy duration at Surgery	*22.21 (13.74)*	*21.86 (13.83)*
FUS frequency (per month)	*13.34 (18.16)*	*10.20 (13.73)*
Number of ASM at surgery	*6.48 (2.65)*	*6.06 (2.54)*

Abbreviations: ASM anti-seizure medication; FUS: focal unaware seizures; fMRI LI: functional magnetic resonance imaging lateralisation index.

Table 3. Language performance before and after temporal lobe resection.

	Language dominant resection		Language non-dominant resection	
Language assessment	*mean (SD)*	Range	*mean (SD)*	Range
Picture naming pre-operative	14.9 (5.5)	4 – 28	17.4 (4.7)	6 – 25
Picture naming 3 months[a]	12.2 (5.2)	1 – 24	17.1 (5.1)	7 – 28
Picture naming 12 months[b]	13.3 (5.2)	2 – 25	17.9 (4.5)	8 – 27
Semantic fluency pre-operative	19.0 (5.6)	5 – 33	18.0 (6.7)	4 – 29
Semantic fluency 3 months[c]	17.2(6.0)	5 – 39	18.7 (4.6)	3 – 30
Semantic fluency 12 months[d]	18.2 (7.0)	6 – 32	20.0 (6.5)	4 – 28
Phonemic fluency pre-operative	14.7 (6.0)	3 – 28	14.8 (5.6)	2 – 36
Phonemic fluency 3 months[c]	13.0 (5.3)	2 – 24	14.9 (5.4)	9 – 32
Phonemic fluency 12 months[d]	13.4 (6.0)	3 – 26	16.4 (5.8)	8 – 36

a. 8/8 language dominant/non-dominant patients missing
b. 20/17 language dominant/non-dominant patients missing
c. 7/4 language dominant/non-dominant patients missing
d. 19/15 language dominant/non-dominant patients missing

Table 4. Summary of the backwards MM-estimate robust linear regression with variables selected based on the RFPE.

	Formula	RFPE
Language Dominant Hemisphere Picture Naming 3 months	GNT3 ~ AFd + Afv + IFG-IFOF + MFG-IFOF + OFC-IFOF + EpLength + RV + LI	0.244
	GNT3 ~ Afd + Afv + IFG-IFOF + OFC-IFOF + EpLength + RV + LI	0.209
	GNT3 ~ Afd + Afv + IFG-IFOF + EpLength + RV + LI	0.201
	GNT3 ~ Afv + IFG-IFOF + EpLength + RV + LI	0.195
	GNT3 ~ IFG-IFOF + Afv + RV + LI	0.1898
	GNT3 ~ IFG-IFOF + RV + LI	**0.1895**
	GNT3 ~ RV + LI	0.244
Language Non-dominant Hemisphere Picture Naming 3 months	GNT3 ~ +MLFa + MFLp + RV + LI	0.141
	GNT3 ~ MLFa + RV + LI	**0.138**
	GNT3 ~ RV + LI	0.149

Abbreviations: AF: arcuate fasciculus; Afd: dorsal sub-fasciculus of the AF; Afv: ventral sub-fasciculus of the AF; EpLength: Epilepsy length at surgery; GNT3: Graded Naming Test at 3 month post-operative; IFG-IFOF inferior frontal sub-fasciculus of the IFOF; IFOF: inferior fronto-occipital fasciculus; OFC-IFOF: Orbital frontal sub-fasciculus of IFOF; MFG-IFOF: Middle frontal sub-fasciculus of IFOF; LI: lateralization index from language fMRI; MLF: middle longitudinal fasciculus; MLFa: anterior sub-fasciculus of the MLF; MLFp: posterior sub-fasciculus of the MLF; RFPE: robust final prediction error; RV: resection volume; EpLength: Epilepsy length at time of operation.

Figures

Figure 1. Scatter plot of language dominant picture naming change at 3 months and the percent of inferior frontal sub-fasciculus of the inferior fronto-occipital fasciculus (*IFG-IFOF) *resection. *Patient outliers were identified by a robust linear regression with the open circles indicating outliers where their weighting in the model was reduced. The dotted horizontal red line indicates the level of significant decline indicated by the reliable change index. Example patient resections are shown as 3D visualizations showing remaining fibers (green) and resected (red) due to resection cavity (blue).*

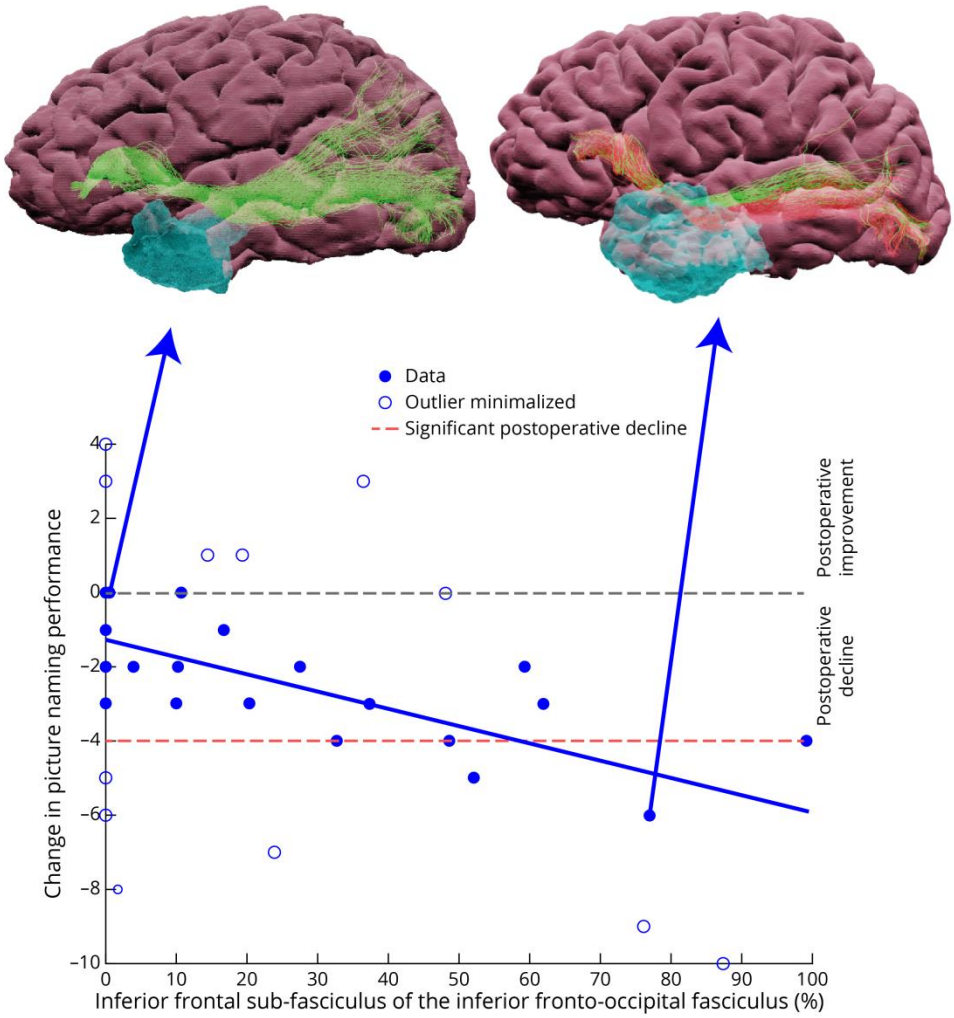

Figure 2. Scatter plot of language non-dominant picture naming score change at 3 months and the percent of the anterior sub-fasciculus of the middle longitudinal fasciculus (*MLFa) *resection. *Patient outliers were identified by a robust linear regression with the open circles indicating outliers where their weighting in the model was reduced. The dotted horizontal red line indicates the level of significant decline indicated by the reliable change index. Example patient resections are shown as 3D visualizations showing remaining fibers (green) and resected (red) due to resection cavity (blue).*

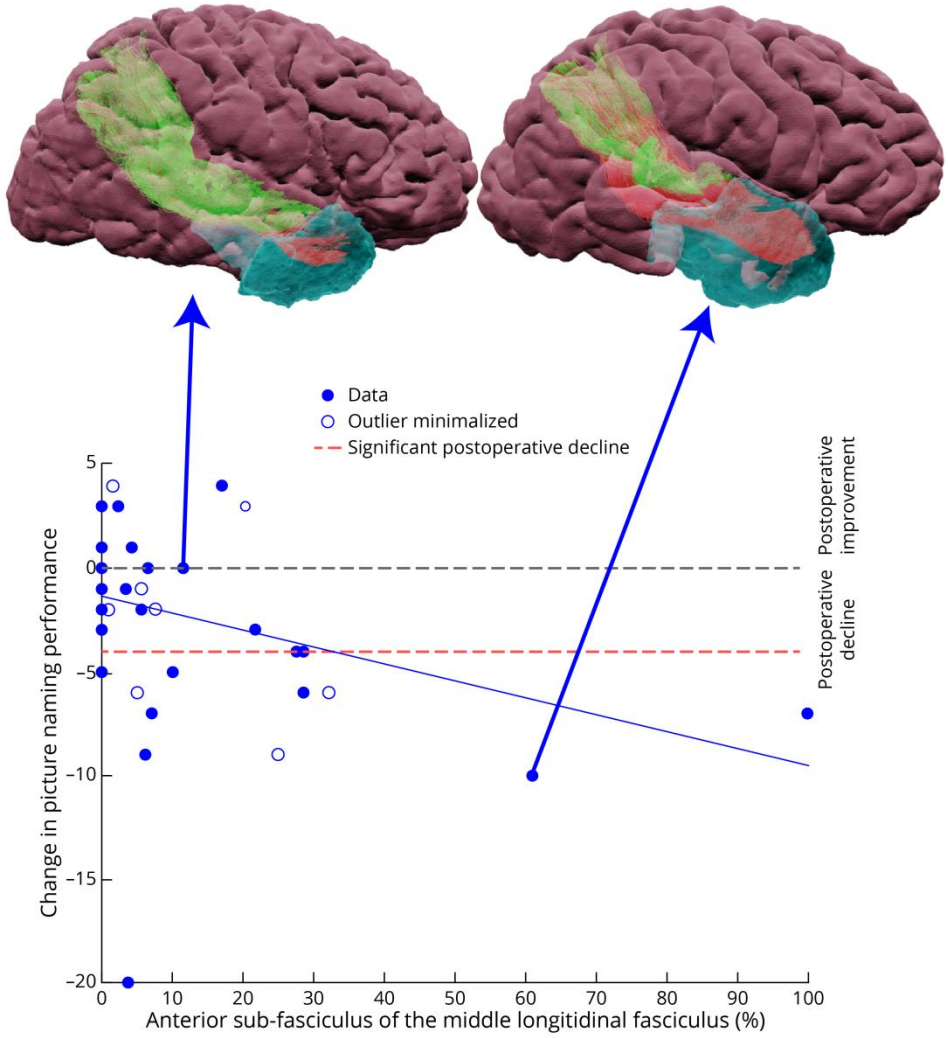

Figure 3. Sagittal representation of a patient with the inferior fronto-occipital fasciculus (a) and middle longitudinal fasciculus (b) spared in left anterior temporal lobe resection. *For each bundle, pre-operative (top) and post-operative (bottom) T1-weighted images are shown with tracts overlaid.*