NATIONAL RESEARCH UNIVERSITY HIGHER SCHOOL OF ECONOMICS

As a manuscript

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STRUCTURAL AND FUNCTIONAL ORGANIZATION OF THE LANGUAGE-RELATED NETWORK IN THE BRAIN IN HEALTHY INDIVIDUALS AND PATIENTS WITH TEMPORAL LOBE EPILEPSY: NEUROIMAGING EVIDENCE

Dissertation Summary

for the purpose of obtaining an academic degree

Doctor of Philosophy in Cognitive Science

Academic Supervisor:

Olga Dragoy, Doctor of Sciences

Moscow 2024

The dissertation was prepared at the Center for Language and Brain at the National Research University Higher School of Economics.

Publications

The ***three*** publications were selected for defense. The author of the dissertation is the first author of all articles:

1. **Karpychev, V.**, Bolgina, T., Malyutina, S., Zinchenko, V., Ushakov, V., Ignatyev, G., Dragoy, O. Greater volumes of callosal sub-regions terminating in language-related areas predict a stronger degree of language lateralization: A tractography study // PLOS One. 2022. Vol. 17. № 12. P. e0276721 (*list A HSE University*, Q2 Web of Sciences / Q1 Scopus).
2. **Karpychev, V.**, Malyutina, S., Zhuravleva, A., Bronov, O., Kuzin, V., Marinets, A., Dragoy, O. Disruptions in modular structure and network integration of language-related network predict language performance in temporal lobe epilepsy: Evidence from graph-based analysis // Epilepsy & Behavior. 2023. Vol. 147. P. 109407 (*list A HSE University*, Q2 Web of Sciences (Behavioral Sciences) / Q2 Scopus).
3. **Karpychev, V.**, Balatskaya, A., Utyashev, N., Pedyash, N., Zuev, A., Dragoy, O., Fedele, T. Epileptogenic high-frequency oscillations present larger amplitude both in mesial temporal and neocortical regions // Frontiers in Human Neuroscience. 2022. Vol. 16. P. 984306v (*list A HSE University*, Q3 Web of Sciences (Neurosciences) / Q2 Scopus (Neurology)).

Conference presentations and public demonstrations of the results.

The results of the studies were discussed at 7 international conferences in 2019-2022:

- 35th International Epilepsy Congress | Virtual Edition (Ireland, 2023). Poster presentation: Language-related changes predict language performance in temporal lobe epilepsy: evidence from graph-based analysis.
- 22nd International Conference on Biomagnetism | Virtual Edition (UK, 2022). Poster presentation: A software platform for comparison of MEG and stereoEEG findings in epilepsy patients.
- 27th Annual Meeting of the Organization for Human Brain Mapping | Virtual Edition (USA, 2021). Poster presentation: IFOF, not the AF, asymmetry predicts functional lateralization for language.
- Psychologie und Gehirn | Virtual Edition (Germany, 2021). Poster presentation: The association of handedness with language lateralization measured by a sentence completion fMRI paradigm in healthy participants.
- 12th Annual Meeting of the Society for the Neurobiology of Language | Virtual Edition (USA, 2020). Poster presentation: No impact of the structural properties of the corpus callosum on handedness: evidence from the constrained spherical deconvolution approach.
- 12th Annual Meeting of the Society for the Neurobiology of Language | Virtual Edition (USA, 2020). Poster presentation: Structural Asymmetry of the Arcuate Fasciculus is not associated with functional lateralization for language, nor with handedness.
- 33rd International Epilepsy Congress (Thailand, 2019). Poster presentation: Pre-surgical evaluation of stereo EEG recordings with high frequency oscillations.

1. Introduction

This dissertation addressed the structural and functional organization of the language-related network, which includes the grey matter structures and white matter tracts involved in language processing, in healthy participants and patients with temporal lobe epilepsy. We considered the association between the white matter structural connectivity and the involvement of left hemisphere language-related network regions and their homologs in language processing in healthy participants. We studied language-related network reorganization by comparing data from healthy participants and people with temporal lobe epilepsy (TLE). Focal seizures in TLE uniquely disrupt functional connectivity both within and outside the temporal lobe. Given that the development of TLE is accompanied by the formation of an epileptogenic network involved in seizure generation, we also estimated the spatial localization of the focus within this network to further compare it with the regions involved in language processing.

It is believed that language processing is provided by a network comprising interconnected regions mainly located in the left hemisphere (Josse, Tzourio-Mazoyer, 2004; Tzourio-Mazoyer, Seghier, 2016). In 10-15% of the healthy population, homologs of left hemisphere regions are also involved in language processing, thus reducing language lateralization and shifting activation during language processing to the right hemisphere (Knecht et al., 2000; Somers et al., 2015). It is related to manual asymmetry – left-hemispheric language activation is more represented in right-handers (about 95%) than in left-handers (about 75%; Knecht et al., 2000; Sommers et al., 2015). However, ontogenetic determinants of these traits of interhemispheric asymmetry differ (Güntürkün, Ocklenburg, 2017). Thus, there are attempts to determine the association of language lateralization with the properties of grey matter structures and white matter tracts (Ocklenburg et al., 2016; 2020).

Given that previous studies did not indicate the association between the properties of grey matter strictures and language lateralization (Tzourio-Mazoyer et al., 2018), it is focused on the interhemispheric interaction carried out via the corpus callosum (CC; Ocklenburg et al., 2016). Hinkley et al. (2016) and Ocklenburg et al. (2015) revealed a language activation shift towards the right hemisphere and, as a result, weaker language

lateralization in people with agenesis of CC. Hence, a larger volume of the CC is thought to lead to stronger language lateralization in the left language dominant hemisphere. It is consistent with the inhibitory model of the interhemispheric interaction, indicating the suppression of the non-dominant hemisphere. On the opposite, the excitatory model suggests that the activation of both hemispheres is supported during language tasks via callosal fibers (Bloom, Hynd, 2005). But how exactly two hemispheres interact during language tasks is unknown.

The investigation of the structural and functional organization of the language-related network is relevant in the scope of TLE (Baciu, Perrone-Bertolotti, 2015). TLE appears as disrupted interactions within and outside the temporal lobe and leads to alterations in cognitive networks (Tracy et al., 2014). Previous studies revealed decreased functional connectivity between regions within the language-related network and increased connectivity with the brain regions that typically are not involved in language processing in healthy people (Roger et al., 2020). In addition, non-language regions were shown to be involved in language processing in both hemispheres (Berl et al., 2014; Foesleitner et al., 2020). Yet, the patterns of language-related network reorganization and their relationship to language performance are unknown (Bullmore, Sporns, 2009; Gerchen et al., 2017).

During the development of TLE, there appears a formation of an epileptogenic network in the brain that is responsible for seizure generation (Bonilha, Keller, 2015). For over 20% of people with TLE, achieving seizure freedom requires surgical removal of the focus of the epileptogenic network (Laxer et al., 2014). However, this network can encompass structures outside the temporal lobe, including areas within cognitive networks such as the language-related network (Caciagli et al., 2023). Therefore, surgery in TLE requires minimizing the removal of the language-related network to preserve language functions. This goal is achieved by precise spatial localization of the epileptogenic network and its focus. The accuracy of focus localization with the current approaches remains insufficient. The current rate of good seizure outcome does not exceed 50-60% of the total number of patients (de Tisi et al., 2011). As a result, surgery

may result in seizure recurrence and make it impossible to minimize tissue removal and, consequently, to preserve the language-related network.

The ***relevance*** of this dissertation is explained by the fact that it is currently unknown how individual differences in the anatomical properties of the CC relate to the involvement of the left hemisphere language-related network regions and their homologs in language processing and how the language-related network can be reorganized in patients with TLE. The methodological constraints of previous studies in reconstructing white matter tracts and considering the CC as an entire group of fibers lead to controversial results in the association with language lateralization. The current analyses of language-related network interactions primarily focus on individual functional connections rather than examining the network as a whole, which has limitations in comprehensively understanding the patterns of language-related network reorganization in TLE. The insufficient accuracy of focus localization in TLE makes it impossible to distinguish the focus from the language-related network, which restricts seizure freedom and preservation of language functions after surgery.

The goals of the study:

- to identify the association between the anatomical properties of the CC (taking into account the heterogeneity of this structure) and language lateralization using cutting-edge tractography applied to diffusion-weighted magnetic resonance imaging (MRI) data.
- to identify alterations related to language-related network reorganization in TLE – adaptation and compensation processes – based on the graph-based analysis applied to functional MRI (fMRI) data during a language task.
- to improve the accuracy of spatial localization of the epileptic focus in TLE using the analysis of high-frequency oscillations and machine learning applied to stereotactic encephalography (sEEG) data.

The ***object*** was the language-related network in healthy participants and patients with TLE. The ***subject*** was the association between the anatomical properties of the CC and language lateralization; alterations in the functional interaction within the language-

related network in patients with TLE; spatial localization of the epileptic focus in people with TLE.

The ***research novelty*** of this dissertation was that, firstly, using advanced tractography based on diffusion-weighted MRI, we confirmed the association between the volume of the callosal sub-region, connecting areas within the language-related network in the temporal and parietal lobes, and language lateralization. Secondly, we compared language-related network organization in healthy participants and patients with TLE via graph-based analysis applied to fMRI during a language task. These alterations in the total language-related network organization in patients with TLE predicted a task performance specific to language processing. Thirdly, high-frequency oscillation analysis and machine learning classification algorithms reveal distinctions in the features of high-frequency oscillations obtained on sEEG data between the focus and other brain regions.

The theoretical significance of the study:

- We confirmed the inhibitory model of the interhemispheric interaction during language processing that leads to language lateralization.
- We established the significance of using advanced tractography based on diffusion-weighted MRI in the white-matter tract reconstruction.
- We showed language-related network reorganization in TLE by the graph-based characteristics that predicted language performance in patients.
- We revealed the significance of the functional connectivity approach (graph theory) to characterize language-related network organization during a task specific to language processing.
- We showed distinctions in the features of high-frequency oscillations between the epileptic focus and the other brain areas in TLE.

The practical significance of the study:

- The results of the study reveal how language functions recover in cases of structural lesions to the language-related areas in the language dominant hemisphere. Such lesions may lead to the involvement of the non-dominant hemisphere areas in language processing via the callosal fibers.

- The results of the study show patterns of language-related network reorganization in TLE and areas of the network that become significant for language processing, which is necessary for surgery.
- The results of the study allow to improve the accuracy of epileptic focus localization in TLE and increase the rate of good surgical outcome.

The ***main results*** of the study and ***provisions*** for the defense:

- Greater volumes of the sub-region, connecting areas within the language-related network in the temporal and parietal lobes, predict a stronger degree of language lateralization. It is consistent with the inhibitory model of the interhemispheric interaction during language processing.
- Patients with TLE exhibited a bilateral module formed by the anterior language-related areas and a module in the left temporal lobe, reflecting hyperconnectivity within the epileptic focus. They did not show a left-lateralized module, including left perisylvian language areas, found in healthy participants. A shift towards the intramodular integration of regions relative to the total network integration of regions relates to language performance and compensation via the increase in the number of connector hubs in the right hemisphere.
- The features of high-frequency oscillations in sEEG differ between the epileptic focus and the other brain areas. This improves the accuracy of focus localization in TLE.

Author contribution

- Study 1: study conception and design, data analyses and interpretation, manuscript draft and revision.
- Study 2: study conception and design, data collection, data analyses and interpretation, manuscript draft and revision.
- Study 3: study conception and design, data analyses and interpretation, manuscript draft and revision.

2. Study 1. An association between volumes of the callosal sub-region and language lateralization

Article selected for the defense:

Karpychev V. et al. Greater volumes of callosal sub-regions terminating in language-related areas predict a stronger degree of language lateralization: A tractography study // PLOS One. 2022. Vol. 17. № 12. P. e0276721.

2.1. Introduction

It was shown that interhemispheric interaction through callosal fibers is related to language lateralization (Gazzaniga, 2000). Adibpour et al. (2018) indicated their role in the development of language lateralization in children with agenesis of CC, which leads to weaker lateralization in adulthood. Thus, the CC contributes to the early development of language asymmetry and maintains it later.

Previous studies examining how the CC relates to language lateralization used either the midsagittal surface in structural T1-images (Josse et al., 2008; Labache et al., 2020; Bartha-Doering et al., 2021) or *diffusion-tensor imaging* (*DTI*) based on diffusion-weighted MRI data (Westerhausen et al., 2006; Putnam et al., 2008; Haberling et al., 2011, Steinmann et al., 2018). However, the restrictions of both methods led to inconsistent results. Furthermore, to study language lateralization, earlier *DTI* was not used to reconstruct separate sub-regions but the whole CC, which is also a constraint given the heterogeneity of callosal fibers (Aboitiz et al., 1992). Thus, in this study, we used *constrained spherical deconvolution* (*CSD*; Dell'Acqua, 2010), which allows us to estimate the volumes and microstructural properties more precisely and, in addition, *DTI* to assess its limitations relative to *CSD*.

We measured language lateralization using fMRI, a technique that allows us to obtain the activation of language-related regions during a language task. As an fMRI paradigm, previous studies used either word generation (Putnam et al., 2008; Haberling et al., 2011; Westerhausen et al., 2006), which activates the anterior language-related regions, or listening (Steinmann et al., 2018), which activates the posterior language-related regions. Thus, each previous *DTI* study reported a result that was based on

language lateralization in either the anterior or posterior language-related areas, but not in both. As a result, distinctions in the associations of the properties of callosal sub-regions and language lateralization in the anterior or posterior language-related areas relied on studies with different groups of participants but not within the same group using the same task. Therefore, we used sentence completion as an fMRI paradigm that reliably activates the anterior and posterior language-related regions (Salek et al., 2017; Wilson et al., 2016; Elin et al., 2022).

The study aimed to compare the volumes and microstructural characteristics of sub-regions of CC using *DTI* and *CSD*, and to test their relations to language lateralization obtained by an fMRI paradigm on sentence completion.

2.2. Method

Fifty healthy individuals (32 females; M_{age} = 24.4, *SD* = 4.8, range = 18-37) participated in the study. According to the Edinburgh questionnaire (Oldfield, 1971), 20 participants with scores between +45 and +100 were classified as right-handed; 10 participants with scores between -45 and +45 were classified as ambidextrous; 20 participants with scores between -100 and -45 were classified as left-handed. All participants performed a language task consisting of experimental (sentence completion) and baseline blocks (syllable repetition). Each block consisted of three stimuli of 5 s duration (the pause between blocks was 2.1 s). In the experimental block, participants had to complete sentences that they read with a semantically and grammatically appropriate word (e.g., "*Now the minister signs an important…*"); in the baseline block, they had to read aloud four times the syllable written on the screen and repeat it once ("*Peeeee peeeeeeeeee peeeeeee peeeeeee…*"). The fMRI session consisted of two runs (120 stimuli – 60 sentences, 60 syllables), lasting 14 min 37 s.

MRI data were acquired using a Siemens 3T Magnetom Verio. We corrected diffusion-weighted MRI for distortions due to eddy currents, subject motion, and phase encoding direction. We applied *DTI* to diffusion-weighted MRI data using the *ExploreDTI* package (http://www.exploredti.com) in MATLAB (MathWorks; Natick, MA, USA). *CSD* reconstruction relied on the Richardson-Lucy algorithm (Dell'Acqua et

al., 2010) with the following parameters: fiber response = 1.5×10^{-3} mm^2/s^{-1}, 400 repetitions, maximum angle for fiber = 30°, seed point resolution = 1 mm^3, step size = 1 mm. We used the *StarTrack* package (https://www.mr-startrack.com/) in MATLAB. We manually reconstructed the CC using the *TrackVis* package (http://trackvis.org/). We subdivided the CC according to a *DTI*-derived scheme, in contrast to other schemes based on structural images of a midsagittal slice of CC (Hofer and Frahm, 2006). The following sub-regions were identified: CC-I, whose fibers project into the prefrontal region; CC-II, premotor and supplementary motor cortex; CC-III, primary motor cortex; CC-IV, primary somatosensory cortex; CC-V, parietal, temporal, and occipital lobes (Hofer, Frahm, 2006; Josse et al., 2008). We extracted the volumes and microstructural properties, *fractional anisotropy (FA)* and *hindrance modulated orientational anisotropy (HMOA)*, for each sub-region in *DTI* and *CSD*, respectively. An example of reconstruction using *DTI* and *CSD* for a subject is shown in Figure 1.

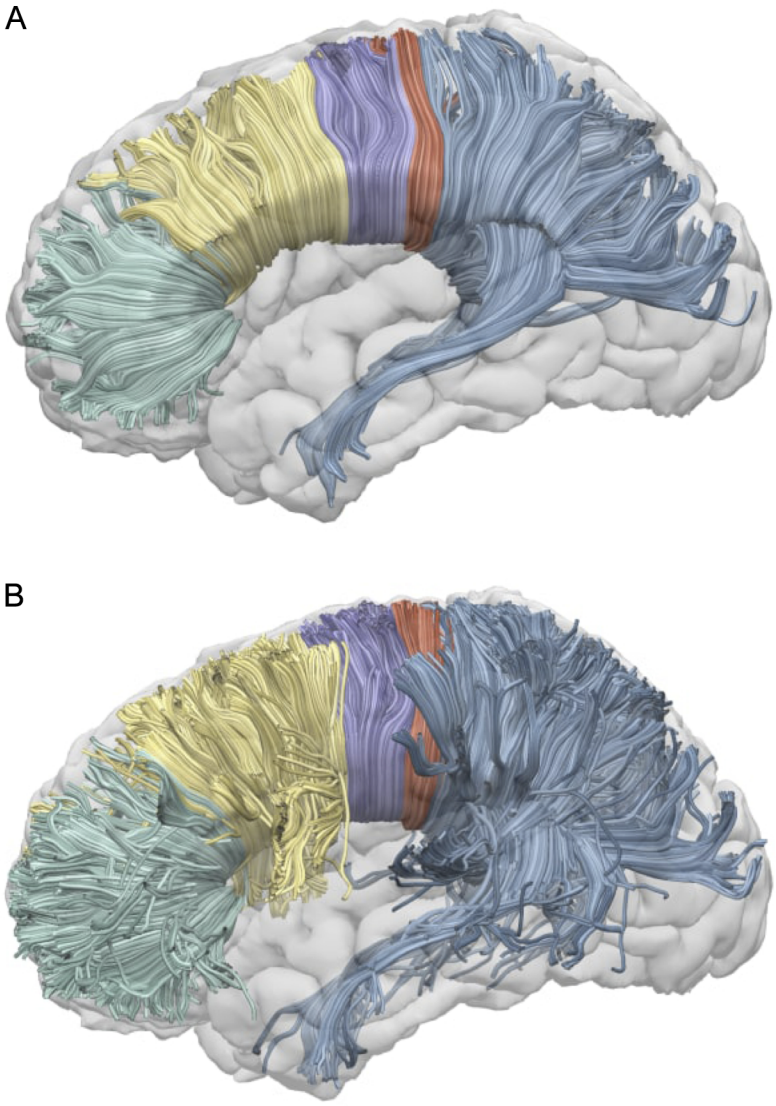

Figure 1. An example of reconstruction using (A) *DTI* and (B) *CSD*.

fMRI data were corrected for distortions due to subject motion and phase encoding direction, aligned relative to the anterior and posterior commissure, and then normalized to the MNI template. We analyzed the fMRI data using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in MATLAB. We performed a first-level analysis to obtain individual activation maps for each participant. We used onset times as the main predictors in the model; the hemodynamic response function for modeling changes in BOLD response. fMRI activation (second-level analysis) for all participatns is shown in Figure 2.

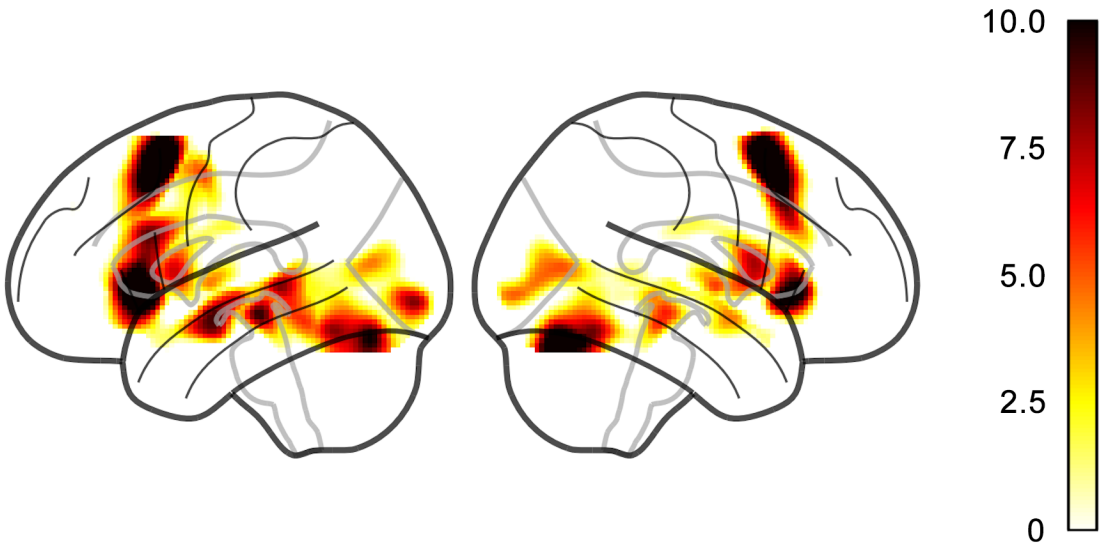

Figure 2. Group map of the language-related activation.

The language *lateralization index* (*LI*) was calculated from individual activation maps using the *LI-toolbox* package (http://www.medizin.uni-tuebingen.de/kinder/en/research/neuroimaging/software/) in SPM12 by the formula:

$$LI = [(A_L - A_R) / (A_L + A_R)],$$

whereby A_L, and A_R – activation of a region in the left and right hemispheres, respectively. We calculated *LI* for grey matter regions corresponding to the sub-regions of the CC in Hofer, Frahm, (2006) – prefrontal region (PFC); premotor and supplementary motor cortex (includes anterior regions of the language network; PM-SMA); primary motor cortex (M_1); primary somatosensory cortex (S_1); parietal, temporal and occipital lobes (includes posterior regions of the language-related network; PTOLs). *LI* ranged from -1 (right-hemispheric asymmetry) to +1 (left-hemispheric asymmetry). Based on Karolis et al. (2019), we used the absolute value of LI_{abs}, thus +1, regardless of hemisphere, indicated strong asymmetry; 0 indicated no asymmetry.

Statistical analyses were performed in JASP (https://jasp-stats.org) and RStudio, version 4.2.0 (https://www.rstudio.com) using the *BayesFactor* package (https://github.com/richarddmorey/BayesFactor). We presented the results of each analysis based on both frequency statistics and Bayesian statistics via BF_{01}. To compare the volumes reconstructed in *DTI* and *CSD*, we used a paired *t*-test (Bonferroni correction, α = .072); to compare microstructural characteristics across sub-regions, we used

ANOVA separately for *FA* and *HMOA* (Bonferroni correction, $\alpha = .025$). To assess the association between LI_{abs} and the properties of each sub-region, we applied multiple linear regression separately for *DTI* and *CSD*.

2.3. Results

For all sub-regions of the CC, volumes were significantly greater in *CSD* than in *DTI*, with evidence in favor of the differences ($BF_{01} > 10^5$). The results are shown in Table 1.

Table 1. Results of paired *t*-tests comparing the volumes of the sub-regions.

Sub-region	Volume in *DTI*		Volume in *CSD*		$t_{(49)}$	*p-value*	BF_{10}
	M	***SD***	***M***	***SD***			
CC-I	16.1	2.7	33.7	9.2	14.36	< 0.001	$> 10^5$
CC-II	18.8	3.4	44.5	12.8	16.09	< 0.001	$> 10^5$
CC-III	9.9	2.2	18.0	5.8	12.26	< 0.001	$> 10^5$
CC-IV	8.5	2.0	14.8	7.0	7.10	< 0.001	$> 10^5$
CC-V	35.3	6.3	67.8	19.8	12.40	< 0.001	$> 10^5$

ANOVA revealed significant differences across all sub-regions in *FA* in *DTI* ($F_{(4,245)} = 94.38$, $p < .001$) and in *HMOA* in *CSD* ($F_{(4,245)} = 86.41$, $p < .001$). $BF_{10} > 10^4$ for both tests showed evidence in favor of significant differences. Post-hoc two-sample *t*-tests (Bonferroni correction, $\alpha = .05/10 = .005$) showed that all sub-regions differed in *FA* in *DTI* except for CC-II and CC-IV ($t_{(49)} = 2.12$, $p = .04$), $BF_{10} = 1.4$; CC-III and CC-V ($t_{(49)} = -2.43$, $p = .02$), $BF_{10} = 1.75$. Post hoc two-sample *t*-tests (Bonferroni correction, $\alpha = .05/10 = .005$) also showed that all sub-regions differed in *HMOA* in *CSD* except CC-III and CC-IV ($t_{(49)} = -1.84$, $p = .07$), $BF_{10} = 0.74$. Figure 3 shows the distribution of *FA* and *HMOA* of sub-regions.

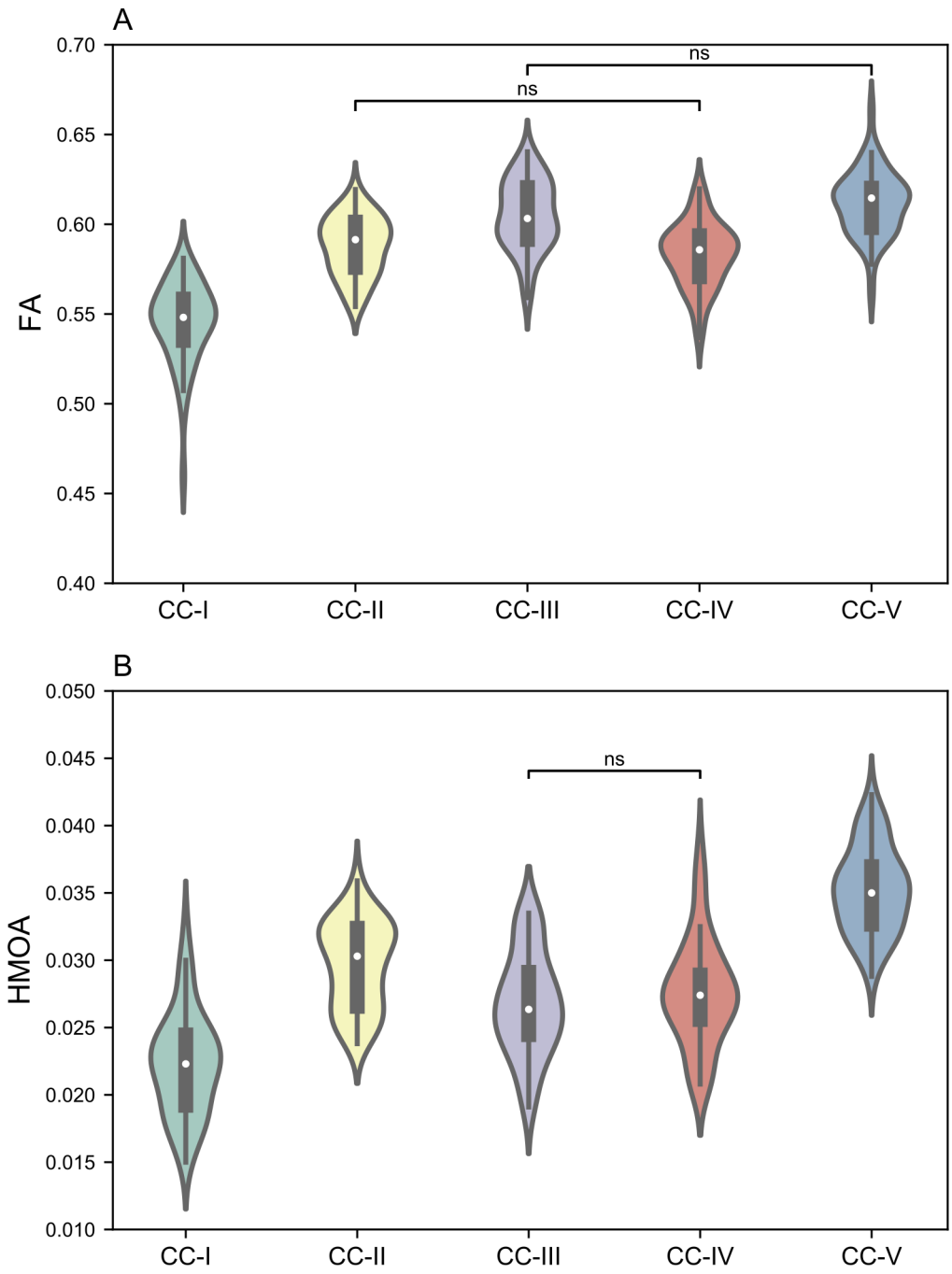

Figure 3. *FA* и *HMOA* across all sub-regions.

Using multiple linear regression models, we found only one significant association between LI_{abs} in PTOLs and the volume of CC-V in *CSD* (β = 4.4, *SE* = 1.4, $t_{(48)}$ = 3.1, p = .003), which reached a level of significance (α = .005), BF_{10} = 4.0. For the rest of the sub-regions in *DTI* and *CSD*, we found no significant relationships with the LI_{abs} of the respective regions.

2.4. Conclusion

To conclude, this is the first study that investigated the relationship between the volumes and microstructural properties of the callosal sub-regions, and the degree of language lateralization using both *DTI* and *CSD*. We found no association between the microstructural properties of the CC and the degree of language lateralization, regardless of the tractography method. In line with the inhibitory model, a greater volume in *CSD*, but not in *DTI*, predicted a stronger degree of language lateralization in cortical areas containing posterior regions of the language-related network in the temporal and parietal lobes. Thus, the association between the sub-regions of the CC and the degree of language lateralization is anatomically specific. In addition, we confirmed that *CSD* is a more suitable approach in tractography as it can reconstruct lateral fibers when lateral crossing projections are in focus.

3. Study 2. Language-related network reorganization in temporal epilepsy.

Article selected for the defense:

Karpychev V. et al. Disruptions in modular structure and network integration of language-related network predict language performance in temporal lobe epilepsy: Evidence from graph-based analysis // Epilepsy & Behavior. 2023. Vol. 147. P. 109407.

3.1. Introduction

An investigation of language-related network reorganization is particularly relevant in TLE (Baciu, Perrone-Bertolotti, 2015). TLE manifests as a disruption of interactions between regions within and outside the temporal lobe, leading to changes in the functioning of cognitive networks, including the language-related network (Tracy et al., 2014; Berl et al., 2014). Previous studies investigating language-related network reorganization used mostly fMRI activation (Balter et al., 2019). However, it does not give us insight into the interaction between regions. Thus, the reorganization in TLE remains poorly understood (Tomasi et al., 2014).

Functional connectivity analysis is an alternative to fMRI activation. This approach estimates the correlational value between time-series of regions to represent their interaction (Friston, 2011). Previous studies examined language-related network reorganization in TLE through functional connectivity but were restricted by the resting-state fMRI data (Doucet et al., 2015). In contrast to the task-based fMRI data (He et al., 2018), the resting-state does not cover all the processes occurring between regions in cognitive networks (Cohen, D'Esposito, 2016). Moreover, previous studies considered individual pairwise connections between regions without describing reorganization at the level of processes occurring in the total language-related network. To complement the previous results, we applied the graph-based analysis, which allows us to describe interactions within the total network, to task-based fMRI data from healthy participants and patients with TLE (Bullmore and Sporns, 2009).

We used sentence completion as a task specific to language processing. It also contrasts ours from previous graph-based fMRI studies, which aimed to activate language and memory networks (Banjac et al., 2021). We believe that it reduces the sensitivity of

the analysis of language-related network reorganization. Thus, we expected that our analysis would provide insights into the reorganization specifically within the language-related network, and the graph-based characteristics would predict the accuracy of the language-related task in people with TLE.

3.2. Method

Twenty-eight patients with drug-resistant left TLE participated in the study (14 females; age: *M* = 37.6, *SD* = 6.2, range = 28–50; age of onset: *M* = 14.3, *SD* = 10.6, range = 0–42; duration: *M* = 21.6, *SD* = 13.3, range = 4–50). MRI indicated sclerosis in the left hippocampus (n = 20; one of these participants also had focal cortical dysplasia in the insular cortex in both hemispheres), sclerosis in both hippocampi (n = 1), gliosis in the left temporal lobe (TL; n = 4), encephaloceles in the left TL (n = 1) or both TLs (n = 1); two participants were MR-negative (n = 2). Nineteen controls with no history of psychiatric or neurological diseases participated in the study (15 females; age: *M* = 40.7, *SD* = 6.5, range = 30–53). All participants were right-handed native Russian speakers. They underwent scanning at the National Medical and Surgical Center named after N.I. Pirogov (Moscow, Russia) and performed a language task described in a previous study (see 2.2. **Method**).

MRI data were acquired using a 3T Siemens Magnetom Skyra. We corrected fMRI data for distortions due to subject motion and EPI using the fMRIPrep-20.2.6 package (https://fmriprep.org/en/20.2.6/#). We regressed out global signal, white matter and cerebrospinal fluid obtained with *aCompCor*. As regions of the language-related network, we considered the 36 regions defined in Labache et al. (2019). We performed the *correlational psychophysiological interaction (cPPI)* analyses on the time-series of the regions to examine the functional connectivity within the experimental block of the language task excluding the baseline block using the *cPPI-toolbox* (https://www.nitrc.org/projects/cppi_toolbox/) in MATLAB. For each participant, we obtained a correlation matrix containing positive correlational coefficients. The correlational coefficients within each matrix were Fisher-transformed to z-scores.

We applied the graph-based analysis to the correlation matrices of healthy participants and patients with TLE to determine how the language-related network was divided into modules; the difference in the integration of regions in the total network, E_{glob}, and within modules, E_{loc}, as well as the difference between them, $IS = E_{glob} - E_{loc}$ (Roger et al., 2020). To assess the integration of regions between modules, we considered connector hubs, regions that are highly functionally connected within their module, and with regions of other modules (Guimerà & Nunes Amaral, 2008). We estimated their number in both hemispheres (N_{hubs}), in the left hemisphere (N_{hubs}-L) and right hemisphere (N_{hubs}-R).

Statistical analyses were performed in RStudio, 4.2.0 (https://www.rstudio.com). We tested differences in E_{glob}, E_{loc}, IS, N_{hubs}, N_{hubs}-L, and N_{hubs}-R between healthy participants and patients with TLE using a two-sample *t*-test for independent samples (Bonferroni correction, $\alpha = .05/6 = .008$). To test the association of language task performance characteristics (*RA* = response accuracy; *RT* = response time), with network characteristics and given their interaction with the duration of epilepsy, we constructed two multiple linear regressions ($\alpha = .05/2 = .025$). Given that IS and N_{hubs} are a linear combination of E_{glob}, E_{loc}, and N_{hubs}-L, N_{hubs}-R, respectively, we used only them in the regressions.

3.3. Results

Figure 4 shows how the language-related network was divided into modules for healthy participants and patients with TLE. The healthy subjects had a left-lateralized module containing anterior and posterior regions of the language-related network, as well as regions in the right temporal pole; patients with TLE showed a bilateral module formed by the anterior language-related areas and a module consisting only of regions of the left temporal lobe – the epileptic focus.

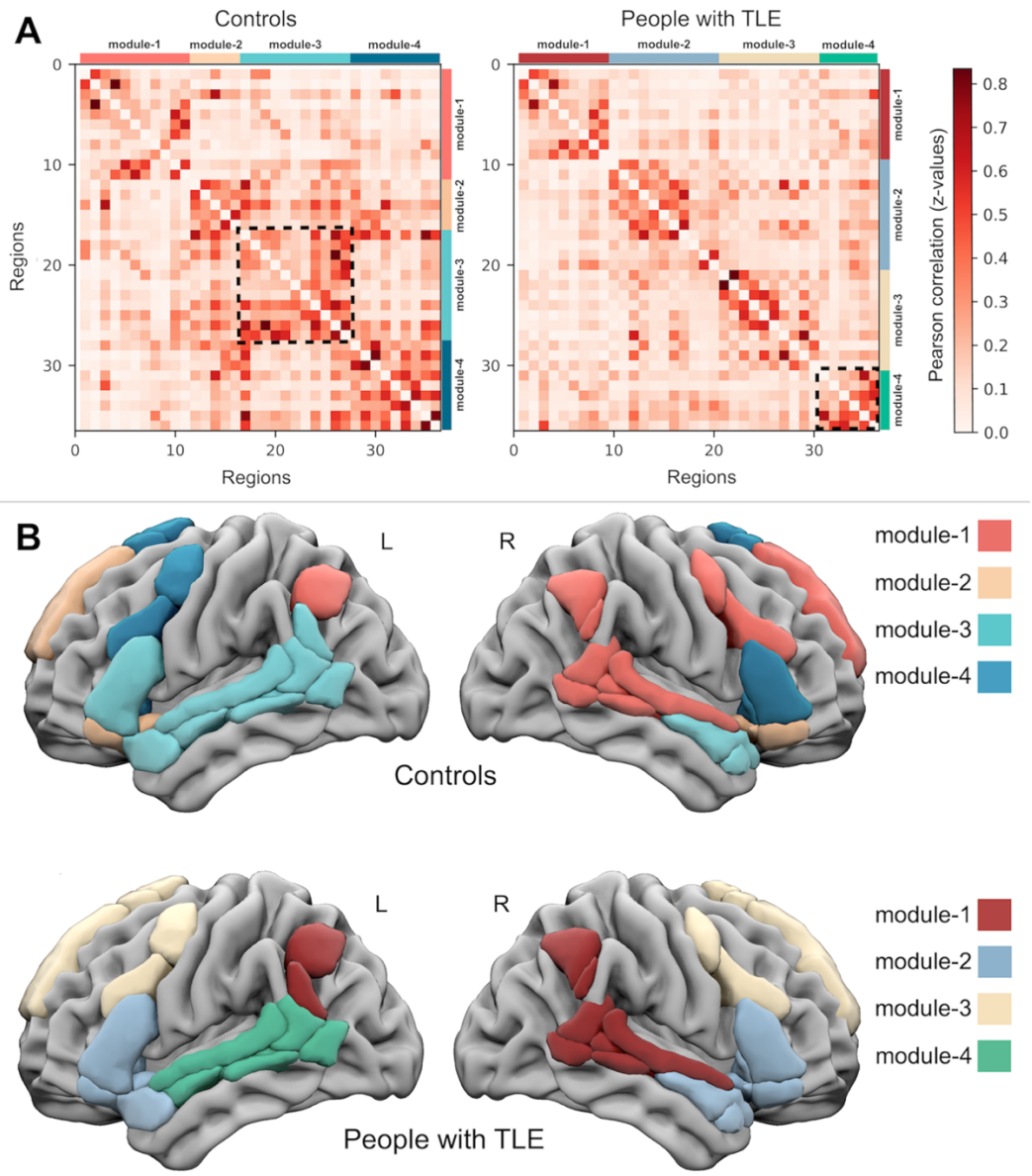

Figure 4. Modular structures of the language-related network in healthy controls and patients with TLE. (A) Connectivity matrices averaged across participants in each group. Dotted squares indicate unique modules for each group: module-3 in healthy controls, and module-4 in people with TLE. (B) Spatial distribution of the modular structure in each group. Each color indicates a single module in each group.

A two-sample *t*-test showed that N_{hubs}-R was significantly lower in healthy participants compared to people with TLE. Differences in *IS* and N_{hubs} reached the significance level of $\alpha = .05$, but not the Bonferroni-corrected level ($\alpha = .05/6 = .008$). In addition to N_{hubs}-R, hubs differed between the two groups. Figure 5 shows their spatial distribution.

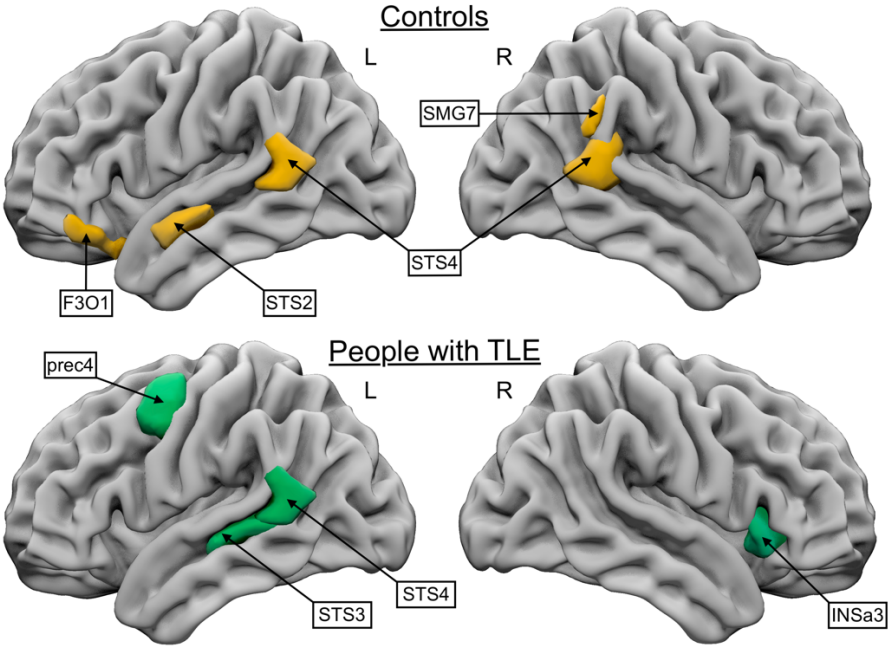

Figure 5. Hubs in healthy controls and people with TLE.

Multiple linear regression showed a significant association between greater *RA* with greater *IS* value ($\beta = 454.4$, $SE = 164.1$, $t_{(14)} = 2.8$, $p = .014$); also with a greater *IS* interaction with duration of epilepsy ($\beta = 580.4$, $SE = 153.0$, $t_{(14)} = 3.8$, $p = .002$) – a decrease in the difference between integration of regions within the total network and integration of regions in modules with epilepsy duration leads to lower *RA*.

3.4. Conclusion

This is the first study aimed at language-related network reorganization in TLE using the graph-based analysis applied to fMRI data acquired during a task that was specific to language processing. During language processing in patients with TLE, a bilateral module formed by the anterior regions of the language-related network and their homologs was identified, as well as a left hemispheric module reflecting the epileptic focus. In contrast to healthy participants, the left hemispheric module containing the anterior and posterior regions of the language-related network, as well as regions in the right temporal pole, was not found in patients with TLE. As a result of such reorganization, for the group of people with TLE, we found that an imbalance towards integration of regions within modules

predicted decreased response accuracy and compensation through the involvement of additional hubs in the right hemisphere.

4. Study 3. Improving the accuracy of focus localization in temporal lobe epilepsy.

Article selected for the defense:

Karpychev V. et al. Epileptogenic high-frequency oscillations present larger amplitude both in mesial temporal and neocortical regions // Frontiers in Human Neuroscience. 2022. Vol. 16. P. 984306.

4.1. Introduction

During the TLE development in the brain, an epileptogenic network appears in the brain that is responsible for seizure generation (Bonilha and Keller, 2015). For over 20% of patients with TLE, achieving good seizure outcome requires surgical removal of this network (Laxer et al., 2014). However, the epileptogenic network can encompass structures outside the temporal lobe, including areas within the language-related network (Caciagli et al., 2023). Therefore, surgery in TLE aims to remove only critical regions within the epileptogenic network – its focus while minimizing the removal of the language-related network. The rate of good surgical outcomes does not exceed 50-60% of the total number of patients (de Tisi et al., 2011). Thus, the accuracy of focus localization using current techniques based on seizure dynamics analysis is insufficient to achieve seizure freedom and reduce the removal of tissue within the language network in TLE to preserve language functions.

High-frequency oscillations (HFO) in EEG, divided into ripples (80-250 Hz) and fast ripples (250-500 Hz; Bragin et al., 1999), are believed to be reliable biomarkers of the epileptic focus in TLE. While *HFO* demonstrated high accuracy in identifying the epileptic focus (van't Klooster et al., 2015; Fedele et al., 2017), both ripples and fast ripples were also detected in other brain regions (Frauscher et al., 2018). To distinguish ripples and fast ripples between the epileptic focus and other regions is thought to be effective to use their morphological features – amplitude, duration, and spectral frequency

(Chen et al., 2021). Previous studies revealed differences in some morphological features between the epileptic focus and other regions but were restricted using univariate statistics (von Ellenrieder et al., 2016).

In this study, we examined *HFO* and their features as biomarkers of the epileptic focus in TLE. We used *machine learning* to classify *HFO* into events occurring within epileptic focus and other regions. The detected *HFO* events were classified into events that appear within the epileptic focus and outside using machine learning.

4.2. Method

Twelve patients with TLE participated in the study (6 women; age: M = 36.9, SD = 11.8, range = 26-69 years; postoperative period: M = 30.5, SD = 11.0, range = 13-44 months). All participants underwent sEEG implantation to detect the epileptic focus and its further removal by surgery at the Pirogov National Medical and Surgical Center. The surgical outcome of the patients was estimated according to the recommendations of the International League Against Epilepsy (ILAE; https://www.ilae.org/). Seizure freedom (ILAE = 1) after surgery was achieved for 11 participants.

To detect ripples and fast ripples in sEEG data from patients during non-REM sleep, we used an automatic detector of *HFO* (Fedele et al., 2017). For each participant, we obtained the distribution of *HFO*-events across all bipolar sEEG channels. We compared the spatial distribution of the epileptic focus (resection area after the surgery) and those channels (*HFO*-channels) whose number of *HFO*-events exceeded the 95% threshold relative to the total number of events across all channels. We defined *HFO*-events as epileptic if *HFO*-channels were within the resection area in patients who reached seizure freedom (ILAE = 1). *HFO*-events across the channels outside the resection area were defined as non-epileptic events occurring in other regions. For all *HFO*-events divided into ripples and fast ripples, we extracted their features – amplitude, duration, and spectral frequency.

We applied the random forest algorithm to build a machine learning model. To train and validate the models, we used a 5-fold cross-validation method consisting of inner and outer cycles (Krstajic et al., 2014). For each model, within each of the five steps

of the inner cycle of internal cross-validation, we used a grid search method to determine the optimal number of decision trees, nodes in each of the trees, and randomly selected features for each of the nodes. We checked the accuracy of the models using the "*area under the error curve" (AUC)*. We extracted the significance of the features for the classification model as the *Gini*-value.

4.3. Results

Figure 6 shows an example of the *HFO*-channels and their comparison with the resection area in a patient with ILAE = 1. For data from 11 patients out of 12, we extracted the morphological features of *HFO*-events to apply machine learning and classify them. Thus, all *HFO*-events (ripples and fast ripples) were divided into two classes: class 1, epileptic events, and class 2, events within the healthy tissues. For the machine learning model, class 1 contained 4,807 events, class 2 - 1,929 events.

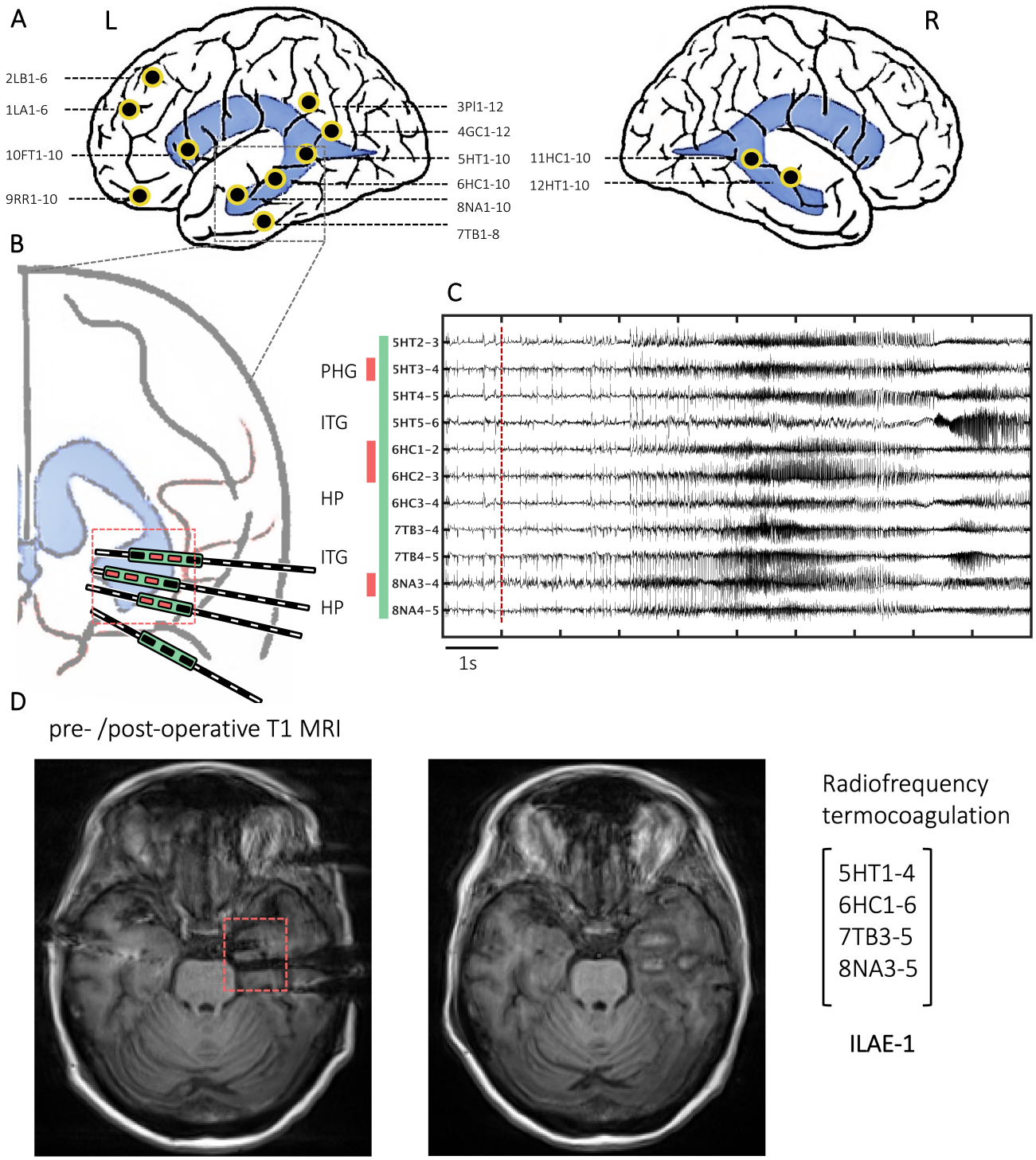

Figure 6. An example of the *HFO*-channels and their comparison with the resection area in a patient (ILAE = 1) (A) spatial distribution of the stereo-EEG electrodes. (B) sEEG channels, defined as *HFO*-channels (red) and resection area (green). The *HFO*-channels were included in the resection region. (C) Stereo-EEG signal during seizure onset (red line). (D) T1-image before and after surgery (thermocoagulation was performed for this participant).

The 5-fold cross-validation method based on the random forest algorithm showed *AUC* = 79.6% (*SD* = 0.8%). For the machine learning model, the most important features for classifying *HFO*-events were the amplitudes of fast ripples (*M* = 0.44, *SD* = 0.05) and ripples (*M* = 0.15, *SD* = 0.03).

4.4. Conclusion

In this study, we showed that the feature of *HFO*-events allows us to classify the events occurring in the epileptic focus and separate them from those occurring in other regions. Our findings can significantly improve current methods of focus localization in patients with TLE, reducing seizure recurrence and minimizing the removal of the language-related network to preserve language functions. The results obtained in this study highlight the importance of considering *HFO* features as a potential biomarker of epileptic focus while studying the reorganization of the language-related network and its separation from the epileptogenic network.

5. Conclusion

This dissertation included articles that focused on the structural and functional organization of the language-related network. We considered the association between CC and language lateralization in healthy participants. We investigated the language-related network reorganization in patients with TLE compared to healthy subjects. We showed how using *HFO* features improves the accuracy of focus localization in TLE. This result can increase the current rate of good seizure outcome in surgery and minimize the removal of the language-related network.

In Chapter 2 (Study 1), we investigated how the structural properties of the CC, reconstructed using tractography, *DTI* and *CSD*, relate to language lateralization. We used a fMRI task specific to language processing for measuring language lateralization. The findings indicated that a larger volume of the callosal sub-region, connecting posterior regions in the temporal and parietal lobes, was associated with a stronger degree of language lateralization. Notably, it was possible to achieve this result using *CSD*, which overcomes the limitations of *DTI* in white matter reconstruction.

In Chapter 3 (Study 2), using the graph-based analysis, we investigated language-related network reorganization in people with TLE characterized by disrupted functional connectivity between regions. Our findings revealed that language-related network reorganization appears as a shift in the modular structure of the total network. Consequently, there emerges an imbalance between the integration of regions across the total network and the integration of regions within modules. This imbalance results in a decline in the accuracy of language task performance. In addition, compensatory mechanisms become evident, such as an increase in the number of hubs in the right hemisphere.

In Chapter 4 (Study 3), we considered the features of *HFO*-events extracted from the sEEG data within the epileptic focus and other regions in patients with TLE. By applying machine learning to classify these *HFO* features, we showed an improvement in focus localization. The most significant feature was the amplitude of the *HFO*-events.

Thus, our findings allowed us to describe language-related network organization in healthy participants and patients with TLE. In addition, we demonstrated an approach to minimize the removal of the reorganized language-related network in TLE.

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