The impact of hippocampal impairment on task-positive and task-negative language networks in temporal lobe epilepsy

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HIGHLIGHTS

- We characterized the impact of unilateral temporal lobe epilepsy (TLE) on the functional connectome during a language task using fMRI.
- In left TLE, a diseased hippocampus is primarily associated with widespread impairment of task-positive language networks.
- In right TLE, an impaired right hippocampus led primarily to a deterioration of connectivity within the default mode network.

ABSTRACT

Objective: To study hippocampal integration within task-positive and task-negative language networks and the impact of a diseased left and right hippocampus on the language connectome in temporal lobe epilepsy (TLE).

Methods: We used functional magnetic resonance imaging (fMRI) to study a homogenous group of 32 patients with TLE (17 left) and 14 healthy controls during a verb-generation task. We performed functional connectivity analysis and quantified alterations within the language connectome and evaluated disruptions of the functional dissociation along the anterior-posterior axis of the hippocampi.

Results: Connectivity analysis revealed significant differences between left and right TLE compared to healthy controls. Left TLE showed widespread impairment of task-positive language networks, while right TLE showed less pronounced alterations. Particularly right TLE showed altered connectivity for cortical regions that were part of the default mode network (DMN). Left TLE showed a disturbed functional dissociation pattern along the left hippocampus to left and right inferior frontal language regions, while left and right TLE revealed an altered dissociation pattern along the right hippocampus to regions associated with the DMN.

Conclusions: Our results showed an impaired hippocampal integration into active language and the default mode networks, which both may contribute to language impairment in TLE.

Significance: Our results emphasize the direct role of the left hippocampus in language processing, and the potential role of the right hippocampus as a modulator between DMN and task-positive networks.

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1. Introduction

A frequent comorbidity in epilepsy is cognitive impairment, which affects the quality of life in these patients. In temporal lobe epilepsy (TLE) due to hippocampal sclerosis (HS), episodic memory...
impairment and language deficits are the most often reported difficulties (Lutz et al., 2004).

TLE is understood as a network disease impacting the distributed language system beyond the seizure focus. Over the recent years, functional magnetic resonance imaging (fMRI) has been established as a means to study cognitive functions in patients with epilepsy. The possibility to analyse functional connectivity (FC) has significantly increased our understanding of epilepsy as a network disease, providing insights about seizure generation and propagation, by studying the neuronal basis of epileptic networks and networks that sub-serve cognitive tasks. Several FC-studies have demonstrated that within the epileptic network functional connectivity was altered, which was also suggested for networks of cognitive function. In both, left and right TLE, FC was reduced within the expressive language network, which was linked to an impaired performance in language assessment (Waites et al., 2006). More recently, during an fMRI naming task stronger connectivity between left posterior inferior temporal and bilateral temporal and frontal lobe regions was associated with improved naming performance (Trimmel et al., 2018).

There is evidence that the hippocampus itself is crucial for language processing (Pai et al., 2016) and it seems to have a key role for widespread cognitive network changes in TLE possibly due to its distributed connections including entorhinal input, fornix output but also the integration in the default mode network (DMN). (Haneef et al., 2014; Englot et al., 2017). Furthermore, resting state fMRI studies have shown that the default mode network includes regions associated with language function particularly in the temporal and frontal lobes (Ye et al., 2011; Gordon et al., 2018) and there is increasing evidence that for successful cognitive task performance successful deactivation of task-negative regions is necessary (Stretton et al., 2012). The relationship to both, task-positive regions associated with general cognitive task performance and task-negative networks as part of the DMN, has been discussed to be functionally dissociated along the hippocampal axis, with anterior regions being stronger connected to regions of the DMN and posterior regions being stronger connected to the task-positive network in healthy controls (Chase et al., 2015). Besides this functional differentiation along the anterior-posterior hippocampal axis, recent studies additionally revealed a functional lateralization effect where only the left hippocampus was attributed to word and language processing, while the right hippocampus was more involved in emotion processing in healthy controls (Plachti et al., 2019).

Today, modern imaging and computational techniques allow the investigation of functional connections, the functional connectome, in addition to the structural connectome to get a complete description of brain connectivity (Biswal et al., 2010). Only recently, the wide-spread impact of TLE on the whole-brain structural (Besson et al., 2014) and functional (Liao et al., 2016) connectome structure has been suggested.

In the present study we used task-based language fMRI and performed complementary ways of connectivity analysis (connectome analysis, functional dissociation analysis) to test the following hypotheses:

1. Alterations of task-positive language networks will be different in patients with left TLE (lTLE) and right TLE (rTLE) compared to healthy controls;
2. Hippocampal connectivity will be impaired in patients with left and right TLE compared to healthy controls, which will impact both, hippocampal integration within the task-positive language network and the DMN;
3. There will be an altered functional dissociation along the anterior-posterior axis of the hippocampi in left and right TLE compared to healthy controls.

This study complements and extends previous findings and will help to further understand language alterations in TLE that may extend beyond the temporal focus.

2. Methods

2.1. Study cohort

We studied 32 patients with medically refractory TLE (17 lTLE, 15 rTLE) due to unilateral HS. All patients underwent evaluation for epilepsy surgery at the Department of Neurology, Medical University of Vienna or the Neurologisches Zentrum Rosenhügel, Vienna. All patients had magnetic resonance imaging (MRI) at 3-Tesla at the Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, including qualitative assessment by expert neuroradiologists revealing unilateral HS and normal contralateral medial temporal lobe structures. The seizure onset in the ipsilateral medial temporal lobe was confirmed with prolonged interictal and ictal video-EEG monitoring. For all patients, presurgical work-up included detailed neuropsychological assessment and language fMRI. At the time of their assessment, all patients were treated with anti-epileptic medication.

To establish a homogeneous study cohort, patients were included according to the following criteria: (1) patients with TLE due to unilateral HS; (2) right-handedness; (3) no other neurological condition in addition to HS (e.g. brain tumor); (4) positive fMRI quality assessment (e.g. adequate task performance, head motion does not exceed 2 mm).

As a control group, 14 individuals with no history of neurologic or psychiatric disease were included. All healthy controls were right-handed and passed fMRI quality assessment. An overview of the study cohorts is given in Table 1. This study was approved by the Ethics Committee of the Medical University of Vienna.

2.2. Out-of-scanner neuropsychological tests

As part of the presurgical work-up all except 4 patients per group completed a phonemic and semantic verbal fluency test and a Boston naming test.

Verbal fluency tests: 60 seconds are given to generate as many words as possible starting with a given letter. Further 60 seconds are given for the subject to produce as many animal names as possible. The performance score is quantified by the number of words correctly generated.

Boston naming test (Kaplan et al., 1983): A well-established word retrieval test which contains 60 line-drawings graded in difficulty that must be named by the subject. The performance is measured by the number of drawings correctly labelled.

For each cognitive test, raw scores were transformed into age adjusted percentiles and in concordance with clinical convention individual percentile ranks from standard deviation (SD) –1.00 to SD 1.00 were defined. Performance below average was defined by SD –1.00, and impaired performance below SD –2.00.

2.3. MRI data acquisition

MRI data was acquired using a 3-Tesla MRI (Philips Medical Systems, Best, Netherlands), equipped with a 12-channel head coil. The imaging session comprised acquisition of a high resolution structural T1-weighted volume (TR/TE 8/3ms, flip angle 8°, 320 × 320 × 195 matrix, voxel size 0.75 × 0.75 × 1 mm); for functional MRI acquisitions an EPI sequence was employed (TR/TE 3000/35 ms, flip angle 90°, 128 × 128 × 32 matrix, voxel size 1.8 × 1.8 × 4 mm3).
Table 1
Overview of the study cohort.

| Subjects | Controls | Left TLE | Right TLE | P-values |
|----------|----------|----------|-----------|----------|
| Gender   | 4/10 (f/m) | 8/9 (f/m) | 3/12 (f/m) | 0.246 |
| Median age (range), years | 39 (31–52) | 41 (15–54) | 44 (23–61) | 0.493 |
| Median duration of disease (range), years | - | 16 (2–39) | 12 (2–48) | Left TLE vs Right TLE: 0.670 |
| Left hippocampus - mean HV (SD) | 0.38 (0.02) | 0.26 (0.05) | 0.38 (0.02) | Left TLE vs Controls: < 0.001 |
| Right hippocampus - mean HV (SD) | 0.39 (0.03) | 0.40 (0.04) | 0.27 (0.05) | Right TLE vs Controls: < 0.001 |
| Language Lateralization | 14 left dominant | 17 left dominant | 15 left dominant | - |

Neuropsychological Tests

| PhoWo – Mean (SD) | 22.67 (11.02) | 21.73 (13.5) | Left TLE vs Right TLE: 0.856 |
| SemiWo - Mean (SD) | 21.92 (7.86) | 22.00 (6.54) | Left TLE vs Right TLE: 0.978 |
| BNT - Mean (SD) | 49.00 (9.08) | 53.45 (3.69) | Left TLE vs Right TLE: 0.145 |

TLE- temporal lobe epilepsy; f – female; m – male; HV - hippocampal volume, quantified with FreeSurfer v5.3 and measured as the percentage of hippocampal volume (cm³) and total brain volume (cm³); SD – standard deviation.
PhoWo – phonemic words; SemiWo – semantic words; BNT – Boston Naming Test.

Statistical tests: Chi squared for gender; ANOVA for age, duration of disease and hippocampal volumes, with Tukey’s Test for post hoc corrections; two sample t-test for neuropsychological values; analysis performed with JASP (https://jasp-stats.org/).

2.4. Functional language task

A clinically well established and frequently used noun-prompted verb generation paradigm (Benjamin et al., 2017) was performed by all subjects. The paradigm was constructed in block design, with 5 blocks consisting of 30 s of rest and 30 s of activation each, resulting in a total scan time of 5 min. The verb-generation task primarily targets language production and consists of German nouns presented for approximately 1 s. Patients were asked to reactively add the task condition to the nuisance regression model.

2.5. Data preprocessing

Data preprocessing was conducted with SPM12, and standard fMRI preprocessing steps were employed. The fMRI data was realigned, where the functional volumes were registered to the mean volume. After slice-timing correction, the fMRI data was co-registered to the anatomical T1 volume, which was used to perform tissue segmentation, including grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The T1 volume was normalized to the MNI space, and the same warp was applied to the co-registered functional data. The fMRI volumes were resampled to 3x3x3mm voxel size, and 6 mm smoothing was applied. Additionally, subject-specific segmentations of the right and left hippocampus were obtained with FreeSurfer v5.3, and manually reviewed and corrected for segmentation errors. The normalization warp was also applied to the hippocampal segmentations, followed by a resampling with nearest-neighbour interpolation to 3 mm, resulting in hippocampal segmentations with 12 coronal slices for each subject.

2.6. Functional connectivity

For FC analysis, the fMRI data was de-noised via nuisance regression including motion parameters, average white matter (WM) and average cerebrospinal fluid (CSF) signal, and their first derivatives, additionally high pass filtering with 0.01 Hz was applied to remove slow drifts. To remove global effects of task onset and to account for underlying neural activity only, we additionally added the task condition to the nuisance regression model (Fair et al., 2007; Kucukboyaci et al., 2013). FC was defined as the fisher-z transformed Pearson’s correlation coefficient between the respective time-series. Nuisance regression and FC-analysis was performed with MATLAB. At second level analysis, connectivity values were corrected for age, sex, hippocampal volume, and duration of disease.

2.6.1. Connectome analysis

To quantify the global impact of TLE on language networks, we performed connectome analysis based on the FC of 360 regions of interest (ROIs) with network-based statistics (NBS) (Zalesky et al., 2010). We used ROIs based on a multimodal parcellation of the cortex, which delineates 360 ROIs associated with 22 distinct cortical communities (Glasser et al., 2016). Connectome analysis was based on non-smoothed fMRI data, and for each ROI the average time-series was used to quantify FC as described above. The assessment of FC was restricted to task condition blocks. In brief, NBS finds connected network components based on a predefined supra-threshold and calculates component-based test statistics. These component-based test statistics are then recalculated multiple times with randomly permuted group memberships, and subsequently compared to the result of the true grouping. We chose a moderate supra-threshold by keeping only connections with a p-value < 0.001 uncorrected, and we used a total number of 50,000 permutations to generate the random baseline distribution.

2.6.2. Hippocampal dissociation

First, we calculated the FC between the average time-series of each of the 12 coronal slices of the subject-specific hippocampal segmentation and every other voxel. Subsequently, for each subject and voxel we correlated the connectivity with its position on the anterior-posterior spatial hippocampal axis. Linear regression resulted in an antero-posterior gradient (ap-gradient) of functional connectivity, describing the functional dissociation within the hippocampus. Positive correlation denotes a linear trend towards a higher connectivity of the posterior parts of the hippocampus to which we refer to as “posterior-dominant ap-gradient”, and negative correlation describes a linear trend towards a higher connectivity of the anterior parts of the hippocampus to which we refer to as “anterior-dominant ap-gradient”. An illustration of the method can be found in Fig. S1 in the supplementary material. Second-level analysis was performed with nonparametric permutation-based threshold-free cluster enhancement (TFCE).
(Smith and Nichols, 2009), with 10,000 random permutations and a corrected family wise error (FWE) rate of 0.05. We performed analysis between groups of controls and patient cohorts. For visualization purpose, results obtained in the MNI volume space were projected to the FreeSurfer surface (Wu et al., 2018).

3. Results

3.1. Neuropsychological assessment

There were no significant group differences in verbal fluency or naming between lTLE and rTLE (Table 1). However, impaired naming was observed in 46.2% lTLE but only 18.2% rTLE patients; impaired semantic verbal fluency was seen in 33.3% lTLE patients, but only 9.1% rTLE patients.

3.2. Imaging results

3.2.1. Connectome analysis

lTLE: Compared to controls, lTLE showed a widespread altered connectome structure with particularly impaired fronto-temporal and fronto-hippocampal connections, involving multiple language relevant regions, including the left superior temporal sulcus (STS), the left inferior frontal cortex (IFC), the dorsolateral prefrontal cortex (DLPFC), frontal insula, and the left temporal-parietal junction (TPJ) (Fig. 1A). We found prominently reduced connectivity between the left IFC and the ipsilateral STS. Reduced connectivity within the DMN was primarily found between regions in the left and right posterior cingulate cortex (PCC) and the right inferior parietal lobe (IPL).

Connectome analysis revealed reduced fronto-hippocampal connectivity of the left hippocampus. Impaired connectivity to the left and right DLPFC was observed, as well as reduced connectivity to regions associated with the core DMN in the anterior cingulate cortex (ACC) and the PCC in the contralateral hemisphere.

rTLE: Compared to controls, right TLE showed less alterations between language relevant regions within the left hemisphere (Fig. 1B), where reduced connectivity was observed mainly within the right temporal lobe but also to contralateral temporal regions and the supplementary motor cortex.

Widespread reduced interhemispheric connectivity was found within the DMN, with the highest amount of reduced connections in the left and right PCC. Also, the right hippocampus showed reduced connectivity to core DMN regions in the contralateral ACC.

3.2.2. Quantification of connectome analyses

In Fig. 1 and Table 2 the anatomical distribution of the node degree of the altered connectome structure is given. In lTLE and compared to controls, the IFC in the left hemisphere (lh) showed a greater number of impaired connections than in the right hemisphere (rh) (40 lh, 24 rh), while less altered connections of language relevant regions were found in rTLE (16 lh, 22 rh).

Fig. 1. Connectome analysis. Connectome analysis revealed distinct patterns of altered connectivity for functional networks of interest in left TLE and right TLE. (A) Compared to controls, in left TLE we observed a widespread altered connectome structure involving multiple language relevant regions (orange), where reduced connectivity between the inferior frontal cortex on the left hemisphere and the ipsilateral STS was most prominent. Little alterations within the default mode network (blue) were found. Reduced connectivity of the left hippocampus was observed (black). (B) In right TLE and compared to controls, we found little alterations between language regions (orange), but greater reduced inter-hemispheric connectivity within the default mode network (blue). Reduced connectivity of the right hippocampus was observed (black). (C) Quantification of the altered connectome structure: Left TLE showed more altered connections between language relevant regions, while in right TLE more connections within the default mode network were impaired. STS - superior temporal sulcus; TLE - temporal lobe epilepsy.
Medial temporal regions showed more altered connections in the left than in the right hemisphere in lTLE (28 lh, 11 rh), whereas in rTLE less impaired connections of the medial temporal lobes were observed (13 lh, 9 rh). Core DMN regions in the PCC and ACC showed a high number of disturbed connections in both patient groups, with particularly the PCC showing the highest number of alterations in rTLE but also ITLE. Overall, patients with left TLE showed more alterations of connections between language relevant regions, while in right TLE more connections within the default mode network were reduced (Fig. 1C).

### 3.2.3. Analysis of hippocampal dissociation

**Left hippocampus:** Compared to controls, ITLE showed a significantly reduced anterior-dominant ap-gradient to the left and to a smaller extent the right IFc, the left middle frontal cortex, and the left motor cortex (Fig. 2A). There were no significant differences between controls and rTLE.

**Right hippocampus:** Compared to controls, ITLE showed a significantly reduced anterior-dominant ap-gradient to the ACC, the precuneus, and the left IPL (Fig. 2B). Patients with rTLE showed a significantly reduced anterior-dominant ap-gradient to the left angular gyrus compared to controls (Fig. 2B).

Overall, we observed a reduced anterior-dominant ap-gradient of hippocampal connectivity in TLE patients compared to healthy controls. Peak voxel coordinates for functional dissociation analysis are displayed in Table S1.

### 4. Discussion

Our analysis revealed that particularly ITLE showed widespread impairment of functional language networks and both, rTLE more than ITLE, showed reduced connectivity within regions associated with the DMN. Further analysis of the hippocampal dissociation along its anterior-posterior axis confirmed disruptions of hippocampal connectivity within both, task-positive and task-negative networks, most likely driven by the diseased hippocampus.

#### 4.1. Impact of hippocampal impairment on language networks in TLE

Cognitive dysfunction, particularly of language and memory, is one of the most common comorbidities in TLE. A wide-ranging effect on the distributed language system has been observed for epileptic foci in the temporal lobe (Duke et al., 2012; Bartha-Doering and Trinka, 2014), including reduced functional connectivity within language networks (Waites et al., 2006). Also, structural connectome analysis revealed widespread structural alterations in the respective temporal lobe and a disconnected fronto-temporal network component in patients with TLE (Besson et al., 2014). Previous studies also supported the hypothesis that the integrity of the hippocampus and fronto-temporal networks was crucial for naming performance in patients with TLE (Bartha et al., 2005a; Bartha et al., 2005b; Bonelli et al., 2011; Bonelli et al., 2012).

In our cohort of ITLE patients a trend towards impaired naming ability was seen. This was paralleled by widespread impaired connectivity of the fronto-temporal language networks within the ipsi- and contralateral hemisphere and which was observed in rTLE to a much lesser extent. This suggests that a diseased left hippocampus affects not only ipsilateral temporal lobe networks but hints at a global disruption of the fronto-temporal language network causing dysfunctions, that may extend beyond the actual seizure focus. This emphasizes the integration of the dominant hippocampus within the language network to ensure proficient language processing.

In ITLE the highest number of reduced connections in the IFC was found in the posterior inferior frontal sulcus (IFSp). This region has been shown to be a central part of the language connectome and it has been proposed that the inferior frontal sulcus plays a key role for word retrieval and word selection (Price, 2010). Therefore, alterations of the language connectome and the reduced naming performance in our left TLE cohort may be due to an impaired word retrieval ability, most likely driven by a disrupted integration of the left IFSp.

#### 4.2. Impact of hippocampal impairment on the Default Mode Network in TLE

A well-studied example of a consistent functional network is the default mode network (DMN), which describes brain areas that

| Community                          | Left TLE < Controls node degree | Right TLE < Controls node degree |
|------------------------------------|---------------------------------|---------------------------------|
|                                    | LH     | RH     | LH     | RH     |
| Primary Visual Cortex              | 3      | 4      | 4      | 3      |
| Early Visual Cortex                | 14     | 9      | 9      | 7      |
| Dorsal Stream Visual Cortex        | 24     | 9      | 17     | 7      |
| Ventral Stream Visual Cortex       | 32     | 42     | 27     | 26     |
| Complex and Neighboring Visual Areas| 7     | 10     | 13     | 9      |
| Somatosensory and Motor Cortex     | 8      | 8      | 4      | 8      |
| Paracentral Lobular and Mid Cingulate Cortex | 26  | 12     | 18     | 10     |
| Premotor                           | 28     | 7      | 10     | 13     |
| Posterior Operculum                | 6      | 10     | 2      | 11     |
| Early Auditory Cortex              | 10     | 5      | 7      | 6      |
| Auditory Association Cortex        | 22     | 22     | 14     | 21     |
| Insular Cortex                     | 19     | 15     | 11     | 23     |
| Medial Temporal Cortex             | 28     | 11     | 9      | 13     |
| Lateral Temporal Cortex            | 18     | 43     | 14     | 15     |
| Temporal-Parietal-Occipital Junction| 11    | 6      | 6      | 15     |
| Superior Parietal and IPS          | 43     | 19     | 18     | 19     |
| Inferior Parietal Cortex           | 14     | 21     | 9      | 19     |
| Posterior Cingulate Cortex         | 26     | 58     | 63     | 64     |
| Anterior Cingulate Cortex          | 31     | 31     | 36     | 20     |
| Orbital and Polar Frontal Cortex   | 13     | 36     | 9      | 5      |
| Inferior Frontal Cortex            | 40     | 24     | 16     | 22     |
| Dorsolateral Prefrontal Cortex     | 24     | 25     | 7      | 19     |

TLE - temporal lobe epilepsy; LH - left hemisphere; RH - right hemisphere.
show greater activity during rest than during engaging cognitive tasks (Greicius et al., 2003). Previous resting state fMRI studies showed that hippocampal connectivity was asymmetric in TLE, with more alterations ipsilateral to the seizure focus (Pereira et al., 2010), while others found similar connectivity changes in both hippocampi (Haneef et al., 2014). Also reduced FC between DMN regions in patients with TLE has been described (Laufs et al., 2007; Cataldi et al., 2013; Haneef et al., 2014).

Our analyses showed reduced connectivity between regions associated with the core DMN, including ACC and particularly the PCC, more prominent in rTLE than lTLE. The hippocampus has been shown to be an integrative part of the DMN (Greicius et al., 2003; Kernbach et al., 2018), and our findings concur with previous studies that showed a reduced hippocampal integration within the DMN in TLE (Haneef et al., 2014; Englot et al., 2016), which was especially evident for the right hippocampus. Several midline brain regions including PCC have been identified as important hub regions for brain network configurations (Dosenbach et al., 2006), and the PCC as an essential hub within the DMN has a key role in modulating interactions between the DMN and cognitive networks essential for task performance (Leech and Sharp, 2014). Therefore, our findings with reduced connectivity for the PCC and other DMN-regions may support observations that cognitive impairment in TLE can be attributed to a deficient network flexibility (Tailby et al., 2018).

4.3. Functional dissociation of the hippocampus in TLE

Previous studies suggested a functional dissociation of the hippocampus (Chase et al., 2015), as well as functional gradients, an emotion-cognition gradient and a self-world-centric processing gradient, along the anterior-posterior axis of the hippocampus (Plachti et al., 2019). Moreover, it was proposed that patterns of functional connectivity even differ along the anterior-posterior axis of each hippocampal subfield (Dalton et al., 2019).

In line with these findings our analysis revealed an anterior-posterior dissociation but also a functional lateralisation of the left and right hippocampus in left and right TLE patients. In rTLE, analysis of the functional dissociation revealed a reduced connectivity for more anterior parts of the right hippocampus to task-positive language regions in the left, and to a lesser extent the right IFC. HS affects primarily the anterior parts of the hippocampus (Blumcke et al., 2013), and the dissociation results emphasize impaired connectivity between anterior parts of the left hippocampus and frontal language regions. While we found no significantly altered dissociation of the left hippocampus in rTLE, for both, lTLE and rTLE, more anterior parts of the right hippocampus showed a reduced connectivity to DMN regions during the verb generation task.

These results suggest that, during the verb-generation task, the right hippocampus is more integrated into the DMN, while the left hippocampus shows a higher integration into the frontal language network, particularly the inferior-frontal cortex.

4.4. Methodological strengths and limitations

Our study has several strengths such as a homogenous group of TLE patients with the same underlying aetiology and connectivity analysis based on task-related experiments, which have demonstrated more reproducibility compared to task-free experiments (Kristo et al., 2014).

There are, however, some limitations. First, many factors such as age at disease onset or neuroanatomical substrates contribute to the (re-)organization of language networks (Wellmer et al., 2009). We considered a selected population of patients with HS, who were all left dominant for language, and the effects of other epilepsy related factors were not investigated in this study. It is necessary to establish patterns of change in a selected, “methodologically idealized” patient population before assessing the input of other potential confounders on language organization.
Second, it is likely that antiepileptic drugs (AEDs) affect functional connectivity (Szaflarski and Allendorfer, 2012). Different combinations of AEDs are a potential confounder also in our patient sample. Future studies are needed to study and disentangle the impact of epileptic seizures versus AEDs on brain networks.

Third, in this study only a trend for reduced naming ability was seen in individual patients with ITLE, a result which is most likely due to small patient numbers. Therefore, we also did not establish a correlation between neuropsychological assessment and connectome patterns; however, future studies are underway focusing on the neuropsychological correlates.

Fourth, the functional dissociation of the hippocampus does not necessarily follow a linear trend, and our correlation analysis is only a simplified model which should be adapted in future work.

5. Conclusion

The hippocampus has been described as an integrative part of the DMN (Greicius et al., 2003; Kernbach et al., 2018), but it also plays an important role in language processing (Piai et al., 2016). Our results suggest that during the verb-generation task, the left hippocampus is more integrated into language networks, particularly the inferior-frontal cortex, emphasizing the direct role of the left hippocampus in language processing: the right hippocampus is integrated into the DMN, emphasizing its potential role as a modulator between DMN and task positive networks, failure of which may indirectly add to language impairment in patients with temporal lobe epilepsy.

Contributors

KHN, SBB: study concept and design, analysis and interpretation of data, manuscript drafting. GG, LBD: analysis of neuropsychological data. OF, ES, MS, VS, CW, SP, CB, DP, EP, GK, GL: established the clinical cohort and contributed clinical data. All authors: critical revision of the manuscript for intellectual content.

Data availability

No data are available due to patient confidentiality issues.

Ethics approval

This study was approved by the Medical University of Vienna Ethics Committee (1883/2016).

Patient consent

Not required.

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Declaration of Competing Interest

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

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.10.031.

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