RESEARCH ARTICLE

Imaging visuospatial memory in temporal lobe epilepsy—Results of an fMRI study

Victor Schmidbauer,1 Karl-Heinz Nenning,1 Michelle Schwarz,2 Olivia Foesleitner,1 Gudrun Mayr-Geisl,1 Mehmet Sahit Yildirim,1 Susanne Pirker,2 Doris Moser,2 Daniela Denk,2 Daniela Prayer,1 Karin Trimmel,2 Georg Langs,1 Christoph Baumgartner,4 Ekaterina Pataraya,2 Gregor Kasprian,1 Silvia Bonelli2*

1 Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria, 2 Department of Neurology, Medical University of Vienna, Vienna, Austria, 3 Department of Neurosurgery, Medical University of Vienna, Vienna, Austria, 4 General Hospital Hietzing with Neurological Center Rosenhugel, Vienna, Austria

* silvia.bonelli@meduniwien.ac.at

Abstract

Purpose
Impairment of cognitive functions is commonly observed in temporal lobe epilepsy (TLE). The aim of this study was to assess visuospatial memory functions and memory-related networks using an adapted version of Roland’s Hometown Walking (RHWT) functional MRI (fMRI) task in patients with TLE.

Methods
We used fMRI to study activation patterns based on a visuospatial memory paradigm in 32 TLE patients (9 right; 23 left) and also within subgroups of lesional and non-lesional TLE. To test for performance, a correlational analysis of fMRI activation patterns and out-of-scanner neuropsychological visuospatial memory testing was performed. Additionally, we assessed memory-related networks using functional connectivity (FC).

Results
Greater contralateral than ipsilateral mesiotemporal (parahippocampal gyrus/hippocampus) activation was observed in left (n = 23)/right (n = 9) TLE. In lesional left TLE (n = 17), significant activations were seen in right more than left mesiotemporal areas (parahippocampal gyrus), while non-lesional left TLE patients (n = 6) showed significant bilateral (left>right) activations in mesiotemporal structures (parahippocampal gyrus). In left TLE, visuospatial cognitive testing correlated with fMRI activations in left (parahippocampal gyrus) and right mesiotemporal structures (hippocampus), characterized by greater fMRI activation being associated with better memory scores. In right TLE, higher scores in visuospatial memory testing were associated with greater fMRI activations in left and right insular regions. FC patterns of memory-related networks differ in left and right TLE.
Conclusion
While TLE in general leads to asymmetrical mesiotemporal activation, lesion-induced and non-lesional TLE patients reveal different memory fMRI activation patterns. In right TLE, insular regions try to compensate for impaired right mesiotemporal structures during the performance of visuospatial tasks. Underlying functional visuospatial memory networks differ in right and left TLE.

Introduction
Temporal lobe epilepsy (TLE) is the most frequent type of focal epilepsy [1] and remains drug resistant in 30% of the cases [2].

If remission of temporal lobe seizures is not achievable by antiepileptic drug treatment, epilepsy-surgery might be an alternative treatment option [1, 3]. A detailed pre-surgical assessment using prolonged video-electroencephalography (EEG) monitoring, neuropsychological and neuropsychiatric evaluation, structural magnetic resonance imaging (MRI), and functional MRI (fMRI) provide important information on the localization of the epileptogenic zone, which has to be removed and essential brain regions [4, 5], which have to be spared during epilepsy-surgery. Hence, precise prediction of the individual outcome after epilepsy-surgery is the ultimate goal of clinical neuroimaging.

Jokeit et al. used fMRI and an adapted version of the Roland's Hometown Walking task (RHWT) [6], in order to investigate hemispheric activation asymmetries in TLE patients [7]. Subjects mentally navigated through their hometown and tried to recall as many details as possible [6, 7]. In healthy subjects, a symmetrical, bilateral activation pattern was observed in mesiotemporal regions. In contrast, TLE patients showed reduced fMRI activations on the side of the seizure focus [7]. The same paradigm provided valuable results for the prediction of visual memory impairment after right-sided temporal lobe resection [8].

Several studies have identified alterations in functional connectivity (FC) among TLE patients [9, 10]. Based on a spatial fMRI task, Doucet et al. demonstrated that left and right TLE patients showed different FC patterns [11, 12]. Adapted versions of the RHWT have been considered, in order to detect differences of fMRI activation patterns in left and right TLE compared to healthy subjects [13]. However, studies using fMRI to investigate memory-related networks in patients with TLE are still scarce.

In this study, we retrospectively analyzed memory fMRI data that were obtained using an adapted version of the RHWT, to assess visual memory fMRI activation patterns in left and right TLE patients and subgroups comparing lesional versus non-lesional TLE.

To test for performance, memory fMRI imaging results were correlated with the results of out-of-scanner neuropsychological testing.

In order to assess functional networks underlying visuospatial memory and how these differ between different TLE groups, task-based FC analysis was performed. As it is currently discussed that the default mode network (DMN) may have a key role during cognitive processing [14], also mesiotemporal integration into anterior and posterior DMN components was analyzed.

This study aims to supply additional information beyond the data provided by Jokeit et al. [7], by investigating visual memory-related activation patterns in TLE patients with different underlying pathologies and particularly non-lesional TLE patients. Furthermore, using...
RHWT-based functional connectivity analysis the present study pursues to identify memory-related networks subserving this task and relevant reorganization mechanisms.

**Materials and methods**

**Ethical approval**

The Ethics Commission of the Medical University of Vienna approved the protocol of this study, which was performed in accordance with the Declaration of Helsinki. All patients gave written informed consent prior to fMRI and agreed to the scientific use of the acquired data.

**Study cohort**

Between 01/2013 and 09/2017, 32 patients (Table 1) with medically intractable TLE underwent memory fMRI, using an adapted version of the RHWT at the Department of Neuroradiology of a tertiary care hospital. Patients were referred for neuroradiological assessment by several Departments of Neurology located in Vienna including two tertiary care centers. All patients underwent (video-)EEG monitoring, structural MRI, and language and memory fMRI. (Video-)EEG monitoring revealed a right seizure onset in 9/32 and a left seizure onset in 23/32 patients. Structural MRI revealed an underlying pathology in 17/23 left and 7/9 right TLE patients. Patients were classified as MRI negative (n = 8), if no structural alteration was detected on MRI. Additionally, in 12 patients results of comprehensive neuropsychological testing including assessment of visuospatial memory functions were available.

| Patient | Pathology/Condition | Hand | Age | Duration | Sex | Language | Seizure Onset |
|---------|---------------------|------|-----|----------|-----|----------|--------------|
| 1b      | HS                  | L    | 41y | 2y       | M   | L        | R            |
| 2b      | HS                  | L    | 54y | 19y      | M   | L        | R            |
| 3b      | HS                  | L    | 34y | 6y       | M   | L        | R            |
| 4b      | GAD+ Encephalitis   | R    | 37y | 3y       | F   | L        | R            |
| 5b      | MCD                 | L    | 19y | 6y       | M   | L        | R            |
| 6a      | Ganglioglioma (16.5x12.8) | R | 39y | 3y       | F   | L        | R            |
| 7a      | MCD                 | R    | 25y | 2y       | M   | Bilateral | R            |
| 8a      | HS                  | R    | 22y | 6y       | F   | L        | L            |
| 9a      | HS                  | R    | 26y | 22y      | M   | L        | L            |
| 10a     | HS                  | R    | 23y | 6y       | F   | L        | L            |
| 11a     | HS                  | R    | 9y  | 4y       | F   | L        | L            |
| 12a     | HS                  | R    | 58y | 52y      | M   | L        | L            |
| 13a     | HS                  | R    | 16y | 5y       | F   | L        | L            |
| 14a     | HS                  | R    | 54y | 35y      | M   | L        | L            |
| 15a     | HS                  | R    | 16y | 16y      | M   | L        | L            |
| 16a     | Oligoastrocytoma (64.3x49.3) | R | 46y | 1m       | M   | L        | L            |
| 17a     | Astrocytoma (72.9x41.4) | R | 29y | 2y       | M   | L        | L            |
| 18a     | Astrocytoma (75.7x41.4) | R | 41y | 2y       | M   | L        | L            |
| 19a     | Cavernoma           | R    | 55y | 1m       | M   | L        | L            |
| 20a     | Cavernoma           | R    | 46y | 3y       | M   | Bilateral | L            |
| 21a     | MCD                 | L    | 42y | 16y      | M   | R        | L            |
| 22a     | Ganglioglioma (38.6x30.7) | R | 18y | 5y       | M   | L        | L            |
| 23a     | DNTE/Astrocytoma (34.1x20.3) | R | 23y | 4m       | F   | L        | L            |
| 24a     | Glioma/DNTE/Ganglioglioma (32.8x14.5) | R | 26y | 1y       | F   | L        | L            |

(Continued)
Groups

Subjects were divided into groups based on the side of the seizure origin and evidence of mesiotemporal pathology:

1. fMRI group activations were compared in left TLE (n = 23) and right TLE (n = 9) (**main activation analysis**). In addition, subgroup analysis was performed in lesioned left TLE (n = 17), lesioned right TLE (n = 7), and left MRI-negative TLE (n = 6) (**subgroup activation analysis**). No subgroup analysis was possible in right MRI-negative TLE patients, due to the small sample size (n = 2). Demographic information of the different groups is given in Table 2. Descriptive statistics were performed using SPSS Statistics for Macintosh, Version 25.0 (IBM Corp, 2017).

2. For correlational analysis with out-of-scanner neuropsychological test results (available in 12 patients) (**S1 Table**), subjects were grouped into lesioned left (n = 6) and lesioned right TLE (n = 6).

---

Table 1. (Continued)

| Patient | Pathology/Condition | Hand | Age  | Duration | Sex | Language | Seizure Onset* |
|---------|---------------------|------|------|----------|-----|----------|----------------|
| 25d     | MRI negative        | R    | 48y  | 3y       | F   | Bilateral| R              |
| 26d     | MRI negative        | R    | 51y  | 11y      | M   | L        | R              |
| 27a     | MRI negative        | R    | 33y  | 4y       | F   | L        | L              |
| 28a     | MRI negative        | R    | 35y  | 2y       | M   | L        | L              |
| 29a     | MRI negative        | R    | 56y  | 1y       | M   | L        | L              |
| 30a     | MRI negative        | L    | 31y  | 24y      | F   | Bilateral| L              |
| 31a     | MRI negative        | R    | 29y  | 24y      | M   | L        | L              |
| 32a     | MRI negative        | X    | 43y  | 15y      | F   | L        | L              |

* Based on video-EEG monitoring and EEG findings

** Lesional right TLE

† Lesional left TLE

‡ Non-lesional right TLE

§ Non-lesional left TLE

Maximum diameters (mm) of (temporal lobe) tumor-related tissue alterations assessed on T2-weighted contrasts (axial plane)

Age: Age at data acquisition

Duration: Period between age at first diagnosis and data acquisition

Hand: Handedness

Language: Language lateralization assessed by clinical language fMRI

Seizure Onset: Hemisphere in which the seizure is generated

DNET: Dysembryoplastic neuroepithelial tumor

F: Female

GAD: Glutamic acid decarboxylase

HS: Hippocampal sclerosis

L: Left

m: Month

M: Male

MCD: Mild malformation of cortical development

MRI: Magnetic resonance imaging

R: Right

X: Unknown

y: Year

https://doi.org/10.1371/journal.pone.0264349.t001
3. FC was analyzed separately in left (n = 23) and right (n = 9) TLE (main functional connectivity analysis). In addition, FC subgroup analysis was performed in lesional left TLE (n = 17), lesional right TLE (n = 7), and left MRI negative TLE (n = 6) (subgroup functional connectivity analysis).

### MRI data acquisition

Imaging data were acquired using a 3 Tesla MRI scanner (Philips Medical System, Best, Netherlands) equipped with a 12-channel head coil. A high resolutional structural T1-image [repetition time (TR)/echo time (TE) = 8/3 ms, flip angle: 8˚, matrix: 320x320x195, voxel size: 0.75x0.75x1 mm] was acquired. An echo planar imaging sequence was used to acquire the fMRI data (TR/TE = 3000/35 ms, flip angle: 90˚, matrix: 128x128x32, voxel size: 1.8x1.8x4 mm) with a duration of 5 minutes.

### fMRI paradigm

For this study, an adapted version of the RHWT was used [6, 7]. Patients were instructed to mentally navigate in a familiar environment and to remember as many details as possible. The task was performed in block design. Activation phases (five cycles) and resting phases (five cycles) lasted for 30 seconds each, for a total duration of five minutes. During the activation phase of the task, subjects were instructed to perform the mental navigation. During the resting phase, patients were instructed to stop mental navigation at the point reached. The task always started with the resting phase, followed by an activation phase. Subjects were asked to keep their eyes closed during the task, in order to minimize visual arousal. Via an intercommunication system, information for starting and stopping the mental navigation was given throughout the process of data acquisition. Patients had to continue mental navigation from that point, where they had stopped in the previous phase. During scanning, task activation was monitored using an online processing tool, which allowed the assessment of incorrect performance of the paradigm. In such cases, the task was explained again and repeated as described above.

### Table 2. Demographic data of the groups.

|                          | Left TLE | Right TLE | Left TLE–Lesional | Right TLE–Lesional | Left TLE–MRI negative |
|--------------------------|----------|-----------|-------------------|--------------------|-----------------------|
| Subjects                 | n = 23   | n = 9     | n = 17            | n = 7              | n = 6                 |
| Sex                      | 9/14 (F/M) | 3/6 (F/M) | 6/11 (F/M)        | 2/5 (F/M)          | 3/3 (F/M)            |
| Handedness               | 20/2/1 (R/L/X) | 5/4 (R/L)  | 16/1 (R/L)       | 3/4 (R/L)          | 4/1/1 (R/L/X)        |
| Median age               | 31 (9–58) | 39 (19–54) | 26 (9–58)        | 37 (19–54)        | 34 (29–56)          |
| Median duration          | 5 (0.083–52) | 3 (2–19)   | 5 (0.083–52)    | 3 (2–19)          | 9.5 (1–24)          |

* Data represented in years complemented by range (in parentheses)

Median age: Median period between age at first diagnosis and data acquisition

F: Female
L: Left
M: Male
MRI: Magnetic resonance imaging
R: Right
TLE: Temporal lobe epilepsy
X: Unknown

[https://doi.org/10.1371/journal.pone.0264349.t002](https://doi.org/10.1371/journal.pone.0264349.t002)
Neuropsychological assessment

Neuropsychological scores for spatial learning and three-dimensional learning, obtained during routine pre-surgical evaluation were used for correlation with fMRI data in this study.

Data of the following neuropsychological tests were used for correlational analysis:

- **Mosaik test**: Coloured building blocks are used to copy a given pattern. The test determines non-verbal conceptualization, visual perception and organization, visual motor coordination, and spatial imagination [15, 16].

- **Maze test**: Subjects must draw the right path through a maze, which tests higher cognitive functions and predictive planning [17, 18].

- **LGT-3 test**: Subjects have to memorize phone numbers, vocabulary, details of a text, city maps, various objects, and symbols. The task determines verbal and spatial skills [19].

- **LPS-7 test**: In several lines, four letters or numbers are printed in different rotations. A fifth character is mirrored and should be recognized and crossed out. The test evaluates spatial perception [20].

Data preprocessing, activation analysis, and correlational analysis

Image preprocessing and data analysis was performed using statistical parametric mapping (SPM) 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and MATLAB R2017a.

Standard fMRI preprocessing was employed. First, fMRI data were motion corrected by realigning each volume to the mean as a reference, and subsequently, co-registered to the structural T1-weighted volume. The T1-weighted images were spatially normalized to the Montreal Neurological Institute (MNI) template space (resolution: 1x1x1 mm), in order to generate comparable data across subjects. Finally, the same normalization transformation was applied to the co-registered functional data, followed by a spatial smoothing with a Gaussian kernel of 8 mm full-width at half maximum.

A two-level random-effect analysis was employed for all imaging data. At the first level, condition specific effects for each subject were estimated with the general linear model (GLM) [21]. For each patient, task-specific effects were estimated via the contrast task against rest. The obtained contrast images were used for the second level group analysis.

At the second level, for each group, a within-group analysis was performed using a one-sample t-test.

In order to test for correlations between areas of fMRI activation and subject’s performance on the Mosaik-, Maze-, LGT-3-, and LPS test simple regression analyses were performed over the whole brain.

fMRI activations were reported at a threshold with a significance level of $p \leq 0.001$ uncorrected/$p < 0.05$ family-wise error (FWE) corrected. Only activations with a cluster size of $\geq 10$ were reported. Due to the small sample size, also non-significant trends were reported for correlational analysis. Special attention was paid to mesiotemporal regions.

Functional connectivity analysis

For FC analysis, data were preprocessed using CONN FC toolbox (18.b) (https://web.conn-toolbox.org). CONN’s “default preprocessing pipeline”was used, involving the following steps: structural segmentation (grey matter, white matter, CSF) and MNI normalization; functional realignment and unwarp (subjects motion estimation and correction); co-registration to the structural image; slice-timing correction; functional outlier detection (global signal z...
threshold: 3; subjects motion threshold: 0.9 mm); functional smoothing (Gaussian kernel filter of 8 mm full-width at half maximum) [22, 23].

Subsequently, a denoising process was performed by applying a band-pass filter (0.008–0.09 Hz), in order to decrease noise and low-frequency drifts.

A region of interest (ROI) to ROI analysis was performed. For this purpose, correlation maps were created for each seed-region in order to calculate significant connectivities between different ROIs [22, 23]. By applying a GLM [21] and bivariate correlation analysis weighted for haemodynamic response function the corresponding correlations were estimated. Fisher’s transformation was applied for all bivariate correlation analysis calculated z-values and correlation coefficients were converted into standard scores. Hence, high z-values between ROIs represent positive correlations and low z-values indicate negative correlations [22, 23].

ROIs were defined by means of CONN’s standard atlas: the Harvard-Oxford atlas for cortical and subcortical regions and the Automated Anatomical Labeling atlas for cerebellar regions [22].

ROI to ROI analysis was performed for each group separately for the active part of the task. Based on previous findings of group activation peaks, the following seed-regions were chosen: right and left parahippocampal gyrus, hippocampus, and insular cortex. Results were corrected with a false discovery rate (FDR) of 5%. Only the most significant connectivities for each region were reported.

Additionally, an independent component analysis (ICA) was performed which allows to extract specific networks for separate assessment [24]. Due to the potential role of the DMN during cognitive tasks [14], mesiotemporal integration into anterior and posterior DMN components was analyzed in each group. CONN uses a group ICA with Back-Projection according to the method proposed by Calhoun et al. [24]. Only the highest significant mesiotemporal values were reported (threshold level at p≤0.001 uncorrected).

**Results**

**Functional MRI–activation analysis**

**Visuospatial memory fMRI activation in left TLE (main activation analysis).** Highly significant activations were found in right mesiotemporal structures [parahippocampal gyrus, posterior division: p(uncorrected)≤0.001, p(FWE) = 0.007, z = 5.17] (Fig 1), but also within extratemporal areas (Table 3).

**Visuospatial memory fMRI activation in right TLE (main activation analysis).** There were significant activations in left mesiotemporal structures [hippocampus: p(uncorrected)≤0.001, z = 3.37] (Fig 1), but also within extratemporal areas (Table 3).

**Visuospatial memory fMRI activation in lesional left TLE (subgroup activation analysis).** Greater activations were found in right [parahippocampal gyrus, posterior division: p (uncorrected)≤0.001, z = 4.49] than left [parahippocampal gyrus, posterior division: p (uncorrected)≤0.001, z = 3.78] mesiotemporal structures, but also within extratemporal areas (Table 4).

**Visuospatial memory fMRI activation in lesional right TLE (subgroup activation analysis).** No significant activations were found in mesiotemporal regions, but mainly in the left inferior temporal and supramarginal gyrus, the left insular and occipital cortex, and right frontal regions (Table 4).

**Visuospatial memory fMRI activation in left MRI negative TLE (subgroup activation analysis).** Significant activations were observed bilaterally in left [parahippocampal gyrus, posterior division: p(uncorrected)≤0.001, z = 3.83] and right [parahippocampal gyrus, posterior division: p(uncorrected)≤0.001, z = 3.73] mesiotemporal structures. Additionally, significant activations were seen in the left fusiform gyrus, the left middle frontal gyrus, and the occipital cortex (Table 4).
Table 3. fMRI activation peaks in left and right TLE.

| Group          | Anatomical Region                              | Coordinates | z-score | \(p\)-value* | FWE      |
|---------------|-----------------------------------------------|-------------|---------|--------------|----------|
| Left TLE (n = 23) | Right intracalcarine cortex                    | 16–62 12    | 6.24    | \(<0.001\)   | \(<0.001\) |
|               | Left precuneus cortex                          | -16–58 12   | 5.60    | \(<0.001\)   | 0.001    |
|               | Right lateral occipital cortex, superior division | 38–76 32   | 5.39    | \(<0.001\)   | 0.003    |
|               | Right parahippocampal gyrus, posterior division | 32–30–14     | 5.17    | \(<0.001\)   | 0.007    |
|               | Left lateral occipital cortex                 | -30–78 30   | 5.02    | \(<0.001\)   | 0.013    |
|               | Left superior frontal gyrus                   | -24 5 56    | 4.99    | \(<0.001\)   | 0.015    |
| Right TLE (n = 9) | Left inferior temporal gyrus, tempororooccipital part | -48–50–12  | 5.49    | \(<0.001\)   | 0.003    |
|               | Left supramarginal gyrus, anterior division     | -42–40 42   | 4.91    | \(<0.001\)   |          |
|               | Left superior frontal gyrus                   | -20–10 64   | 4.86    | \(<0.001\)   |          |
|               | Left lateral occipital cortex, superior division | -44–66 22   | 4.50    | \(<0.001\)   |          |
|               | Left middle temporal gyrus, tempororooccipital part | -50–56 2    | 4.39    | \(<0.001\)   |          |
|               | Left cingulate gyrus                          | -14–36 34   | 4.17    | \(<0.001\)   |          |
|               | Left precuneus cortex                         | -22–54 8    | 4.09    | \(<0.001\)   |          |
|               | Right superior frontal gyrus                  | 28 6 64     | 4.04    | \(<0.001\)   |          |
|               | Left hippocampus                              | -28–20–16   | 3.37    | \(<0.001\)   |          |

* Uncorrected \(p\)-values
FWE: Family-wise error corrected
MRI: Magnetic resonance imaging
TLE: Temporal lobe epilepsy

Fig 1. Visuospatial memory fMRI activation in left and right TLE. In left TLE (a), significant fMRI activations were observed in right (cross-hair in a: parahippocampal gyrus (coordinates: 32–30–14), posterior division; \(p\) (FWE) = 0.007) mesiotemporal regions. In contrast, right TLE patients (b) showed greater fMRI activation in left mesiotemporal regions (cross-hair in b: hippocampus (coordinates: -28–20–16); \(p\) (uncorrected)\(<0.001\). Images are displayed at a threshold level at \(p\)<0.05 (FWE) (a)/\(p\)<0.001 (uncorrected) (b) (left: left hemisphere; right: right hemisphere).

https://doi.org/10.1371/journal.pone.0264349.g001

Correlational analysis with out-of-scanner neuropsychological test results

Correlational analyses in lesional left TLE. Significant correlations were observed exclusively in left mesiotemporal areas (parahippocampal gyrus, posterior division; \(p\)
characterized by greater fMRI activation being associated with better performance during the Mosaik test. Better performance during the LGT-3-, LPS-7-, and Maze test was associated with greater fMRI activations in right mesiotemporal regions (Table 5).

**Correlational analyses in lesional right TLE.** No significant correlations between mesiotemporal fMRI activations and out-of-scanner neuropsychological testings were found. Instead, significant correlations were observed between fMRI activation in the left insular cortex and scores of the LGT-3-, LPS-7-, and Mosaik test characterized by greater activation being correlated with better performance. Furthermore, significant correlations were found between fMRI activations in the right insular cortex and frontal operculum and better performance during the Mosaik test (Table 5). No significant correlations were seen for the Maze test.

### Functional connectivity analysis

**ROI to ROI analysis.** For better characterization of the underlying visuospatial memory networks, seed-based FC analysis was performed.

Fig 2 gives an overview of the connectivity patterns in left and right TLE.
Left TLE (main functional connectivity analysis). In left TLE, significant connectivities were observed between the left/right parahippocampal gyrus and contralateral temporal areas and to extratemporal regions. However, there was greater connectivity between right parahippocampal regions to frontal areas as compared to the contralateral side. There was strong connectivity between the left/right hippocampus and contralateral temporal areas and to extratemporal regions. Negative correlations (anticorrelations) were found, predominantly, between the left hippocampus and frontal lobe areas. Both left and right insular cortex revealed widespread connectivity to ipsilateral and contralateral frontal, temporal, parietal, and occipital areas. Detailed information is given in the S1 Text.

Right TLE (main functional connectivity analysis). In right TLE, there were significant connectivities between ipsilateral and contralateral mesiotemporal areas. However, there was poor connectivity between mesiotemporal regions and extratemporal areas. Negative correlations (anticorrelations) were observed within left temporal regions. Both left and right insular cortex revealed widespread connectivity to ipsilateral and contralateral brain regions. Detailed information is given in the S2 Text.

Lesional left TLE (subgroup functional connectivity analysis). In lesional left TLE, significant connectivities were observed between the left and right parahippocampal gyrus and contralateral mesiotemporal areas. There were considerable connectivities between mesiotemporal regions and parietal areas. However, as opposed to the right parahippocampal gyrus, the left parahippocampal gyrus showed reduced connectivity to extratemporal regions. Negative correlations were observed, predominantly, between the left hippocampus and frontal areas. Both left and right insular cortex revealed widespread connectivity to ipsilateral and contralateral frontal, temporal, parietal, and occipital areas. Detailed information is given in the S3 Text.

Lesional right TLE (subgroup functional connectivity analysis). In lesional right TLE, significant connectivities were observed between left mesiotemporal areas and extratemporal regions. Negative correlations were observed within left temporal areas. Both left and right insular cortex revealed strong connectivity to temporal regions. Detailed information is given in the S4 Text.

Left MRI negative TLE (subgroup functional connectivity analysis). In non-lesional left TLE, significant connectivities were observed within mesiotemporal regions, primarily originating from the right hippocampus. As opposed to the left insular cortex, right insular areas revealed a more complex connectivity pattern. Detailed information is given in the S5 Text.

---

### Table 5. Correlational analyses with neuropsychological data.

| Group                      | Test             | Anatomical Region                              | Coordinates | z-score | p-value * |
|----------------------------|------------------|-----------------------------------------------|-------------|---------|-----------|
| Lesional left-sided TLE (n = 6) | Mosaik test     | Left parahippocampal gyrus, posterior division | -26–40–12   | 4.01    | ≤0.001    |
|                            | Mosaik test     | Right hippocampus                              | 22–12–22    | 2.68    | 0.004     |
|                            | Maze test       | Right hippocampus                              | 32–10–16    | 3.14    | 0.001     |
|                            | LPS-7 test      | Right parahippocampal gyrus, posterior division | 32–32–10    | 2.88    | 0.002     |
|                            | LGT-3 test      | Right parahippocampal gyrus, posterior division | 34–32–10    | 3.08    | 0.001     |
| Lesional right-sided TLE (n = 6) | LGT-3 test      | Left insular cortex                            | -32 16 2    | 4.17    | ≤0.001    |
|                            | LPS-7 test      | Left insular cortex                            | -26 26 0    | 4.00    | ≤0.001    |
|                            | Mosaik test     | Right frontal operculum                        | 48 14–4     | 4.77    | ≤0.001    |
|                            | Mosaik test     | Left insular cortex                            | -28 26–2    | 4.48    | ≤0.001    |
|                            | Mosaik test     | Right insular cortex                           | 40 16–4     | 4.28    | ≤0.001    |

* Uncorrected p-values

TLE: Temporal lobe epilepsy

https://doi.org/10.1371/journal.pone.0264349.t005
Independent component analysis. In order to specifically assess how mesiotemporal structures are linked to the DMN and how this may secondarily alter task-positive cognitive networks ICA was performed.

Left TLE (main functional connectivity analysis). In left TLE, there was integration of both left and right parahippocampal gyrus, posterior division [left: \(p(\text{uncorrected}) \leq 0.001, z = 6.32\); right: \(p(\text{uncorrected}) \leq 0.001, z = 6.26\)] within the posterior DMN, while there was only right mesiotemporal integration [hippocampus: \(p(\text{uncorrected}) \leq 0.001, z = 4.45\)] within the anterior DMN (Fig 3).

Right TLE (main functional connectivity analysis). In right TLE, there was integration of left mesiotemporal structures [parahippocampal gyrus, posterior division: \(p(\text{uncorrected}) \leq 0.001, z = 4.25\)] within the posterior DMN. However, with regard to the anterior DMN, no mesiotemporal integration was observed (Fig 3).
Lesional left TLE (subgroup functional connectivity analysis). In lesional left TLE, integration of both left and right hippocampus [left: \( p \) (uncorrected) \( \leq 0.001, z = 4.263 \); right: \( p \) (uncorrected) \( \leq 0.001, z = 4.33 \)] within the posterior DMN was observed. As opposed to that, there was only right mesiotemporal integration [right hippocampus: \( p \) (uncorrected) \( \leq 0.001, z = 4.214 \)] within the anterior DMN.

Lesional right TLE (subgroup functional connectivity analysis). In lesional right TLE, integration of left mesiotemporal structures [left parahippocampal gyrus, posterior division: \( p \) (uncorrected) \( \leq 0.001, z = 7.247 \)] within the posterior DMN was found. However, with regard to the anterior DMN, no mesiotemporal integration was observed.

Left MRI negative TLE (subgroup functional connectivity analysis). In non-lesional TLE, ICA did not reveal mesiotemporal integration within the anterior or posterior DMN.

Discussion

Summary of main findings

In this study, we retrospectively analyzed memory fMRI data based on an adapted version of the RHWT in order to investigate visuospatial memory function in TLE patients. We used a paradigm that required different components of memory functions, however, visuospatial memory components were primarily relevant for performing this task adequately.

In all patients, we demonstrated activations within frontoparietal, temporal, or occipital areas as part of the visuospatial memory network. In (lesional) left and right TLE relatively greater activation was seen in contralateral mesiotemporal structures, while in subjects with non-lesional left TLE, bilateral mesiotemporal activations were observed.

Furthermore, we showed that in patients with lesional left TLE, higher scoring in visuospatial neuropsychological testing was correlated with fMRI activations exclusively within right and left mesiotemporal structures. In lesional right TLE, a significant correlation was observed within extratemporal regions in both, left and right insular regions.
Connectivity analysis revealed reduced mesiotemporal FC in right compared to left TLE patients.

**Visual memory fMRI in TLE**

fMRI is considered a promising pre-operative tool for assessing the lateralization and localization of memory function and to estimate the post-surgical risk of impairment [7, 8, 25, 26]. Furthermore, fMRI can be useful for assessing memory reorganization processes in TLE patients [27]. In line with findings of a previous study by Jokeit et al. [7], we demonstrated greater fMRI activations in mesiotemporal regions contralateral to the seizure onset zone in patients with (left and right) TLE. Compared to findings in healthy controls, who demonstrated symmetrical, bilateral mesiotemporal activations during the task, this is most likely due to the underlying pathology or even indicates reorganization processes [7] within temporal or extratemporal regions such as the insular cortex.

Most of the previous studies focused on reorganization processes in lesion-induced TLE. Very few descriptions exist about memory reorganization in subjects with non-lesional TLE [28]. In this study, subgroup analyses revealed that MRI negative left TLE patients showed bilateral activation patterns in mesiotemporal regions similar to those that have been described in healthy controls. Lateralization of the seizure onset zone in TLE patients has extensively been investigated by means of EEG, neuroimaging, and proton magnetic resonance spectroscopy [29]. Good concordances of the results of the different modalities were observed in subjects with lesional TLE. However, this was not applicable to non-lesional TLE. Results of spectroscopy studies revealed integrity of mesiotemporal structures on the side of the seizure focus in MRI negative TLE [29]. This may also explain the presence of bilateral fMRI activation in the left-sided MRI negative TLE group. However, there are also task-based and resting-state fMRI studies showing a reduced blood oxygenation level dependency (BOLD) signal in non-lesional TLE on the side of the seizure focus [28, 30]—presumably due to the ongoing epileptic activity. Compared to lesional TLE, however, non-lesional TLE patients showed less lateralized patterns of fMRI activations.

**Neurobiological and clinical implications**

**Functional reorganization within visuospatial memory networks.** In left TLE patients, higher scoring during neuropsychological visuospatial memory testing was associated with greater fMRI activations exclusively in right > left mesiotemporal regions. Many descriptions indicate that, primarily, right mesiotemporal regions are involved in visual and spatial perception, which is in keeping with our findings [31, 32]. However, for the Mosaik test, significant correlations were found in the left parahippocampal gyrus, supporting the hypothesis that both left and right mesiotemporal structures are involved in visuospatial memory processing [33].

In right TLE, we did not observe significant activations in mesiotemporal structures. However, higher scoring during the LPS-, LGT-3-, and Mosaik test was associated with greater fMRI activations in the left insular cortex. Additionally, better performance during the Mosaik test was associated with activations in the right insular cortex and the right frontal operculum. The insular region has been associated with many different functions, such as cognition, attention, and visual and motor control [34, 35]. We suggest that damage to key structures in the right mesiotemporal lobe triggers reorganization processes, leading to activation of insular and opercular regions during visuospatial processing. The insular cortex has a key role during various cognitive tasks and shows multiple and complex connections to different brain areas [36]. Especially the left insular cortex is thought to be involved in several brain networks and might
serve as a junction for different information [37]. This could explain our findings of insular involvement in visuospatial memory functions, since the insular cortex might support right mesiotemporal structures after damage. Lee et al. demonstrated that visuospatial memory performance did not differ before and after right-sided mesiotemporal surgical intervention in right TLE patients [38], which might point to the existence of multiple extratemporal systems supporting visuospatial memory function. However, further studies are needed in order to confirm our findings and to clarify the role of insular regions in visuospatial memory function.

Impairment of visuospatial memory networks and the DMN in TLE. In both, left and right TLE, mesiotemporal structures showed strong connectivity to contralateral and ipsilateral areas located within and outside the mesial temporal lobe. Overall, mesiotemporal regions in right TLE patients revealed reduced connectivity patterns compared to subjects with left TLE. This is in keeping with previous studies that showed that diminutions of limbic FC were more severe in right-sided than left-sided TLE patients [11, 39].

Reduced connectivity between left temporal regions and frontal areas has been described in left TLE and has been proposed to be associated with memory loss and language impairment [39]. However, it has also been speculated that the reduction of FC between the diseased temporal lobe and frontal areas might help in preserving cognitive functions, in terms of a memory protection mechanism by downregulation of a devastated network [11]. In our study, strong connectivity was observed between right mesiotemporal structures and frontal areas in left TLE, possibly indicating a compensatory upregulation of the contralateral memory network.

In left TLE, strong connectivity was also detected between the left insula and right temporal lobe areas, which was similarly observed in right TLE with the left insula being strongly connected to left temporal areas, underlining the driving role of left insular regions for visuospatial memory function. The connectivity pattern between the right insula and temporal regions was almost similar in right and left TLE patients, underpinning the integration of insular regions within visuospatial memory networks.

The FC subgroup analysis in lesional left and right TLE revealed comparable results to the main analysis. However, interestingly, non-lesional left TLE patients showed stronger connectivity within right hemispheric areas. Thus, although these patients demonstrate more bilateral/ipsilateral fMRI activation patterns during the RHWT, as opposed to lesion-induced TLE, the underlying visuospatial memory network exhibits a more rightward pattern. These findings underscore the complexity of memory reorganization processes in MRI negative TLE patients [28].

Using ICA, decreased involvement of mesiotemporal structures, particularly of hippocampal regions ipsilateral to the seizure onset zone into the DMN was revealed. The DMN is considered to decrease its activity during the active performance of a task [14]. Nonetheless, there is also evidence that the DMN serves as an active component during task execution [40] and, therefore, also may have a significant role as a part of memory-related brain networks [14]. Our findings are in keeping with previous findings in the literature [41] underlining the potential role of the DMN during active memory processing, showing reduced integration of right→left mesiotemporal structures into the DMN [40, 41]. FC changes appear to have a negative impact on a variety of cognitive and social skills, especially in right-sided TLE. As demonstrated in a previous study, it could be shown that disruptions of right limbic networks, predominantly detectable in right TLE, interfere with social-cognitive abilities [42].

In non-lesional TLE, there was no (para)hippocampal integration during task execution, which might indicate differences in mesiotemporal DMN component downregulation/
upregulation mechanisms during cognitive processing in these patients as compared to subjects with lesion-induced TLE. Thus, our data may suggest differences in DMN involvement during active task execution in lesional (left/right) and MRI negative TLE. Nonetheless, further studies are needed to clarify the role of the DMN during active cognitive processing in patients with TLE.

**Limitations**

Our study has several limitations. No healthy controls were available for the current study, which prohibited a direct comparison between TLE patients and healthy subjects. However, information regarding activation patterns in healthy subjects in this study was based on data previously described by Jokeit et al. [7].

Due to the retrospective nature of the study, the overall number of patients investigated with the RHWT was relatively small with different underlying pathologies and differences in disease duration. This has been addressed by dividing patients into subgroups with lesional and non-lesional left or right TLE. Further studies will be needed to define the role of epilepsy-related variables, such as underlying pathology, lesion localization, etc. on the organization of memory function.

In this study, we report findings based on uncorrected p-values, because the small sample influences statistical power and renders multiple comparison correction too strict. Although FWE/FDR correction is pivotal to reduce the occurrence of type I error, there is evidence of an increased type II error rate contemporaneously, primarily, with respect to modest samples [43]. Where applicable, we report uncorrected results with a conservative threshold (p<0.001), entailing caution in the interpretation of our findings. The small sample and the absence of healthy controls limited an SPM-based/CONN-based between group-comparison and the possibility to detail pathology-related fMRI activation/FC differences. However, a qualitative approach was used to detect fMRI activation-based/FC-based between-group differences.

Neuropsychological data was not available in all our patients. Therefore, correlational analyses were performed only in a subgroup of patients with lesional TLE. Findings will need to be confirmed in larger patient samples and further studies are underway, in order to address reorganization mechanisms of verbal and visual memory functions in larger patient cohorts with heterogeneous pathologies.

**Conclusion**

Memory fMRI paradigms using adapted versions of the RHWT can be used for the assessment of visuospatial memory processing and its reorganization in TLE. While TLE in general leads to asymmetrical mesiotemporal activation, lesion-induced and non-lesional TLE patients reveal different fMRI activation patterns during the performance of the task. Furthermore, our data indicate that within the visual memory network insular regions serve as supporting brain areas in case of right mesiotemporal damage. Based on the data presented in this study, one can conclude that functional memory networks differ in right and left TLE.

**Supporting information**

S1 Table. Neuropsychological data. (DOCX)

S1 Text. ROI to ROI: Left TLE. (TXT)
S2 Text. ROI to ROI: Right TLE.
(TXT)

S3 Text. ROI to ROI: Lesional left TLE.
(TXT)

S4 Text. ROI to ROI: Lesional right TLE.
(TXT)

S5 Text. ROI to ROI: Non-lesional left TLE.
(TXT)

Author Contributions

Conceptualization: Olivia Foesleitner, Gregor Kasprian, Silvia Bonelli.

Data curation: Victor Schmidbauer, Michelle Schwarz, Olivia Foesleitner, Gudrun Mayr-Geisl, Mehmet Salih Yildirim, Susanne Pirker, Doris Moser, Daniela Denk, Ekaterina Pataraia.

Formal analysis: Victor Schmidbauer, Karl-Heinz Nenning, Gudrun Mayr-Geisl, Silvia Bonelli.

Investigation: Michelle Schwarz, Ekaterina Pataraia, Gregor Kasprian, Silvia Bonelli.

Methodology: Victor Schmidbauer, Karl-Heinz Nenning, Georg Langs, Gregor Kasprian, Silvia Bonelli.

Project administration: Daniela Prayer, Christoph Baumgartner, Gregor Kasprian.

Resources: Daniela Prayer, Christoph Baumgartner, Ekaterina Pataraia, Gregor Kasprian.

Software: Karl-Heinz Nenning, Daniela Prayer, Georg Langs, Gregor Kasprian.

Supervision: Karl-Heinz Nenning, Susanne Pirker, Doris Moser, Daniela Denk, Karin Trimmel, Georg Langs, Christoph Baumgartner, Ekaterina Pataraia, Gregor Kasprian, Silvia Bonelli.

Validation: Gudrun Mayr-Geisl, Silvia Bonelli.

Visualization: Victor Schmidbauer, Karl-Heinz Nenning.

Writing – original draft: Victor Schmidbauer.

Writing – review & editing: Karl-Heinz Nenning, Michelle Schwarz, Olivia Foesleitner, Gudrun Mayr-Geisl, Mehmet Salih Yildirim, Susanne Pirker, Doris Moser, Daniela Denk, Daniela Prayer, Karin Trimmel, Georg Langs, Christoph Baumgartner, Ekaterina Pataraia, Gregor Kasprian, Silvia Bonelli.

References

1. Te`llez-Zenteno JF, Hernández-Ronquillo L. A review of the epidemiology of temporal lobe epilepsy. Epilepsy Res Treat. 2012; 2012:630853. https://doi.org/10.1155/2012/630853 PMID: 22957234

2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000; 342:314–319. https://doi.org/10.1056/NEJM200002033420503 PMID: 10660394

3. de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WFJ, Sander JW, et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet. 2011; 378:1388–1395. https://doi.org/10.1016/S0140-6736(11)60890-8 PMID: 22000138

4. Iwasaki M, Jin K, Nakasato N, Tominaga T. Non-invasive evaluation for epilepsy surgery. Neurol Med Chir (Tokyo). 2016; 56:632–640. https://doi.org/10.2176/nmc.ra.2016-0186 PMID: 27627857
5. Rosenow F, Lüders H. Presurgical evaluation of epilepsy. Brain. 2001; 124:1683–1700. https://doi.org/10.1093/brain/124.9.1683 PMID: 11522572

6. Roland PE, Eriksson L, Stone-Elander S, Widen L. Does mental activity change the oxidative metabolism of the brain? J Neurosci. 1987; 7:2373–2389. PMID: 3612246

7. Jokeit H, Okujava M, Woermann FG. Memory fMRI lateralizes temporal lobe epilepsy. Neurology. 2001; 57:1786–1793. https://doi.org/10.1212/wnl.57.10.1786 PMID: 11723264

8. Janszky J, Jokeit H, Kontopoulou K, Mertens M, Ebner A, Pohlmann-Eden B, et al. Functional MRI predicts memory performance after right mesiotemporal epilepsy surgery. Epilepsia. 2005; 46:244–250. https://doi.org/10.1111/j.0013-9580.2005.10804.x PMID: 15679505

9. Englot DJ, D’Haese P-F, Konrad PE, Jacobs ML, Gore JC, Abou-Khalil BW, et al. Functional connectivity disturbances of the ascending reticular activating system in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry. 2017; 88:925–932. https://doi.org/10.1136/jnnp-2017-315732 PMID: 28630376

10. Sidman N, Chaitanya G, He X, Doucet G, Kim NY, Sperling MR, et al. Task activation and functional connectivity show concordant memory laterality in temporal lobe epilepsy. Epilepsy Behav. 2018; 81:70–80. https://doi.org/10.1016/j.yebeh.2018.01.027 PMID: 29499551

11. Doucet G, Osipowicz K, Sharan A, Sperling MR, Tracy JL. Hippocampal functional connectivity patterns during spatial working memory differ in right versus left temporal lobe epilepsy. Brain Connect. 2013; 3:398–406. https://doi.org/10.1089/brain.2013.0158 PMID: 23705755

12. Bernhardt BC, Hong S, Bernasconi A, Bernasconi N. Imaging structural and functional brain networks in temporal lobe epilepsy. Front Hum Neurosci. 2013; 7:624. https://doi.org/10.3389/fnhum.2013.00624 PMID: 24098281

13. Towgood K, Barker GJ, Caceres A, Crum WR, Elwes RD, Costafreda SG, et al. Bringing memory fMRI to the clinic: comparison of seven memory fMRI protocols in temporal lobe epilepsy. Hum Brain Mapp. 2015; 36:1595–1608. https://doi.org/10.1002/hbm.22726 PMID: 25727386

14. Raichle ME. The brain’s default mode network. Annu Rev Neurosci. 2015; 38:433–447. https://doi.org/10.1146/annurev-neuro-071013-014030 PMID: 25938726

15. Rogowski S. Therapieassozierte kognitive Funktionstörungen und deren psychometrische Erfassung bei Patienten mit primären Gehirntumoren. 1st ed. Disserta-Verlag Hamburg; 2017.

16. Tewes U. HAWIE-R: Hamburg-Wechsler-Intelligenztest für Erwachsene, Revision 1991. Huber-Verlag Bern; 1991.

17. Kircher T, Gauggel S. Neuropsychologie der Schizophrenie: Symptome, Kognition, Gehirn. 1st ed. Springer-Verlag Berlin Heidelberg; 2008.

18. Porteus SD. The maze test and clinical psychology. 1st ed. Pacific Books Palo Alto, CA; 1959.

19. Amelang M, Schmidt-Atzert L. Psychologische Diagnostik und Intervention. 4th ed. Springer-Verlag Berlin Heidelberg; 2006.

20. Horn W. Leistungsprüfsystem (LPS). 2nd ed. Hogrefe-Verlag Göttingen; 1983.

21. Friston KJ, Holmes A, Worsley K, Poline J, Frith C, Frackowiak R. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp. 1995; 2:189–210.

22. Porcu M, Craboledda D, Garofalo P, Barberini L, Santillippo F, Zaccagna F, et al. Reorganization of brain networks following carotid endarterectomy: an exploratory study using resting state functional connectivity with a focus on the changes in Default Mode Network connectivity. Eur J Radiol. 2019; 110:233–241. https://doi.org/10.1016/j.ejrad.2018.12.007 PMID: 30599866

23. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012; 2:125–141. https://doi.org/10.1089/brain.2012.0073 PMID: 22642651

24. Calhoun VD, Adali T, Pearlson GD, Pekar JJ. A method for making group inferences from functional MRI data using independent component analysis. Hum Brain Mapp. 2001; 14:140–151. https://doi.org/10.1002/hbm.1048 PMID: 11559959

25. Bonelli SB, Powell RH, Yogarajah M, Samson RS, Symms MR, Thompson PJ, et al. Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection. Brain. 2010; 133:1186–1199. https://doi.org/10.1093/brain/awq006 PMID: 20157009

26. Schacher M, Haemmerle B, Woermann FG, Okujava M, Huber D, Grunwald T, et al. Amygdala fMRI lateralizes temporal lobe epilepsy. Neurology. 2006; 66:81–87. https://doi.org/10.1212/01.wnl.0000191303.91188.00 PMID: 16401851

27. Limotai C, McLachlan RS, Hayman-Abello S, Hayman-Abello B, Brown S, Bihari F, et al. Memory loss and memory reorganization patterns in temporal lobe epilepsy patients undergoing anterior temporal lobe resection, as demonstrated by pre-versus post-operative functional MRI. J Clin Neurosci. 2018; 55:38–44. https://doi.org/10.1016/j.jocn.2018.06.020 PMID: 29934057
28. Muhlhoffer W, Tan Y-L, Mueller SG, Knowlton R. MRI-negative temporal lobe epilepsy—what do we know? Epilepsia. 2017; 58:727–742. https://doi.org/10.1111/epi.13699 PMID: 28266710
29. Zhang J, Liu Q, Mei S, Zhang X, Liu W, Chen H, et al. Identifying the affected hemisphere with a multimodal approach in MRI-positive or negative, unilateral or bilateral temporal lobe epilepsy. Neuropsychiatr Dis Treat. 2014; 10:71–81. https://doi.org/10.2147/NDT.S56404 PMID: 24476628
30. Reyes A, Thesen T, Wang X, Hahn D, Yoo D, Kuzniecky R, et al. Resting-state functional MRI distinguishes temporal lobe epilepsy subtypes. Epilepsia. 2016; 57:1475–1484. https://doi.org/10.1111/epi.13456 PMID: 27374869
31. Abrahams S, Morris RG, Polkey CE, Jarosz JM, Cox TC, Graves M, et al. Hippocampal involvement in spatial and working memory: a structural MRI analysis of patients with unilateral mesial temporal lobe sclerosis. Brain Cogn. 1999; 41:39–65. https://doi.org/10.1006/brcg.1999.1095 PMID: 10536085
32. Bohbot VD, Kalina M, Stepankova K, Spackova N, Petrides M, Nadel L. Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia. 1998; 36:1217–1238. https://doi.org/10.1016/s0028-3932(97)00161-9 PMID: 9842767
33. Burgess N, Maguire EA, O’Keefe J. The human hippocampus and spatial and episodic memory. Neuron. 2002; 35:625–641. https://doi.org/10.1016/s0896-6273(02)00830-9 PMID: 12194864
34. Menon V, Uddin LO. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010; 214:655–667. https://doi.org/10.1007/s00429-010-0262-0 PMID: 20512370
35. Yeung AWK. The 100 most cited papers concerning the insular cortex of the brain: a bibliometric analysis. Front Hum Neurosci. 2018; 12:337. https://doi.org/10.3389/fnhum.2018.00337 PMID: 30210323
36. Cavalcante LES, Zinn CG, Schmidt SD, Saenger BF, Ferreira FF, Furini CRG, et al. Behav Brain Res. 2017; 334:129–134. https://doi.org/10.1016/j.bbr.2017.07.044 PMID: 28760699
37. Gogolla N. The insular cortex. Curr Biol. 2017; 27:R580–586. https://doi.org/10.1016/j.cub.2017.05.010 PMID: 28633023
38. Lee TM, Yip JT, Jones-Gotman M. Memory deficits after resection from left or right anterior temporal lobe in humans: a meta-analytic review. Epilepsia. 2002; 43:283–291. https://doi.org/10.1046/j.1528-1157.2002.09901.x PMID: 11906514
39. Haneef Z, Lenartowicz A, Yeh HJ, Levin HS, Engel J Jr, Stern JM. Functional connectivity of hippocampal networks in temporal lobe epilepsy. Epilepsia. 2014; 55:137–145. https://doi.org/10.1111/epi.12476 PMID: 24313997
40. Vatansever D, Menon DK, Manktelow AE, Sahakian BJ, Stamatakis EA. Default mode network connectivity during task execution. Neuroimage. 2015; 122:96–104. https://doi.org/10.1016/j.neuroimage.2015.07.053 PMID: 26220743
41. James GA, Tripathi SP, Ojemann JG, Gross RE, Drane DL. Diminished default mode network recruitment of the hippocampus and parahippocampus in temporal lobe epilepsy. J Neurosurg. 2013; 119:288–300. https://doi.org/10.3171/2013.3.JNS121041 PMID: 23706058
42. Tollgren H, Adhimoolam B, Rankin KP, Hupperz HJ, Kurthen M, Joekitt H. Right fronto-limbic atrophy is associated with reduced empathy in refractory unilateral mesial temporal lobe epilepsy. Neuropsychologia. 2015; 78:80–87. https://doi.org/10.1016/j.neuropsychologia.2015.09.010 PMID: 26363299
43. Lieberman MD, Cunningham WA. Type I and Type II error concerns in fMRI research: re-balancing the scale. Soc Cogn Affect Neurosci. 2009; 4:423–428. https://doi.org/10.1093/scan/nsp052 PMID: 20035017