Face-name association task reveals memory networks in patients with left and right hippocampal sclerosis☆

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ARTICLE INFO

ABSTRACT

We aimed to identify reorganization processes of episodic memory networks in patients with left and right temporal lobe epilepsy (TLE) due to hippocampal sclerosis as well as their relations to neuropsychological memory performance.

We investigated 28 healthy subjects, 12 patients with left TLE (LTLE) and 9 patients with right TLE (RTLE) with hippocampal sclerosis by means of functional magnetic resonance imaging (fMRI) using a face-name association task, which combines verbal and non-verbal memory functions. Regions-of-interest (ROIs) were defined based on the group results of the healthy subjects. In each ROI, fMRI activations were compared across groups and correlated with verbal and non-verbal memory scores.

The face-name association task yielded activations in bilateral hippocampus (HC), left inferior frontal gyrus (IFG), left superior frontal gyrus (SFG), left superior temporal gyrus, bilateral angular gyrus (AG), bilateral medial prefrontal cortex and right anterior temporal lobe (ATL). LTLE patients demonstrated significantly less activation in the left HC and left SFG, whereas RTLE patients showed significantly less activation in the HC bilaterally, the left SFG and right AG. Verbal memory scores correlated with activations in the left and right HC, left SFG and right ATL and non-verbal memory scores with fMRI activations in the left and right HC and left SFG.

The face-name association task can be employed to examine functional alterations of hippocampal activation during encoding of both verbal and non-verbal material in one fMRI paradigm. Further, the left SFG seems to be a convergence region for encoding of verbal and non-verbal material.

1. Introduction

Hemispheric lateralization of memory within the mesial temporal lobe (mTL) has been the subject of functional MRI studies for many years. According to the classic material-specific model, the dominant (usually the left) mTL predominates in mediating verbal memory functions (Frisk and Milner, 1990) and the non-dominant (usually the right) mTL in non-verbal or visual memory functions (Kelley et al., 1998; Smith and Milner, 1981). However, this rather strict view had to be weakened as more and more studies emerged documenting postoperative verbal memory decline in patients after right temporal resection (Gleissner et al., 2002; Saling, 2009; Sidhu et al., 2016). For the non-verbal domain, there is even less evidence for a strict lateralization to the right mTL. Literature rather suggests an involvement of both mTL in visuo-spatial memory (Glikmann-Johnston et al., 2008; Saling, 2009; Sidhu et al., 2016). Instead of the classical material-specific model dynamic interactions between both mTL depending on specific task demands have been suggested (Saling, 2009).

The understanding of memory processes within the mTL is of particular importance with regards to memory outcome after anterior temporal lobe resections in patients with temporal lobe epilepsy (TLE) as it is known that surgery within the mTL bears the risk of relevant losses in episodic memory function. Patients with good memory abilities prior to surgery are especially more likely to decline in memory performance than patients with poor preoperative memory (Gleissner et al., 2004). Therefore, functional reorganization processes in patients with mTL damage and TLE have been the focus of many fMRI studies in recent years. It became apparent that TLE patients tend to reorganize their verbal and non-verbal memory functions to the contralesional mTL

(Alessio et al., 2013; Banks et al., 2012; Cheung et al., 2009; Milian et al., 2015; Powell et al., 2007; Richardson et al., 2003; Sidhu et al., 2013).

Only few studies, however, have investigated reorganization processes within the whole brain. Alessio et al. (2013) found evidence of a more diffuse and bilateral cortical representation of verbal memory functions in left TLE (LTLE) patients, especially in the middle and ventro-lateral frontal regions, but also occipital, parietal and temporal areas, as compared to right TLE (RTLE) patients and healthy controls. Using a visual memory paradigm, they were able to demonstrate in RTLE patients more widespread and bilateral areas of activations than in LTLE patients and healthy controls during the encoding, but not the retrieval stage. Altered memory networks in TLE patients have also been reported by Sidhu et al. (2013), who were able to demonstrate that patients with LTLE recruited more contralateral regions, especially in the frontal and temporal lobe during word and face encoding, whereas RTLE patients engaged the middle frontal gyrus bilaterally during word encoding but showed activity increases only within the temporal lobes during face encoding as compared to healthy controls. Both studies used two material-specific paradigms for verbal and non-verbal memory functions, i.e. encoding of words to investigate left mTL memory functions and abstract drawings or faces for the assessment of right mTL memory functions. Using different paradigms to assess memory reorganization in left and right TLE patients is burdensome for the patients due to the necessity of longer scanning times and also renders direct comparison between both patient groups difficult.

In the current study, we investigated the networks underlying verbal and non-verbal memory functions in left and right TLE patients with hippocampal sclerosis (HS) compared to healthy subjects based on one paradigm that can address both right and left mTL memory functions within a unified framework. Therefore, we performed an fMRI study in patients with left and right TLE as well as healthy controls using a face-name association task. This task was designed to address both verbal and non-verbal memory functions relatively equally as face-name associations have been shown to rely on both mTLs and elicit bilateral hippocampal activations in healthy subjects (Kirwan and Stark, 2004; Klamer et al., 2013; Sperling et al., 2003).

The aims of our study were: (i) To test the hypothesis that LTLE and RTLE patients show less activation than healthy subjects within the respective hippocampus (HC) affected by sclerosis. (ii) To investigate whether responses in other brain areas involved in face-name encoding in healthy participants also exhibit altered activations in LTLE and RTLE patients. (iii) Finally, we addressed whether activation in these areas is behaviourally relevant and can predict memory performance as demonstrated by correlations between hemodynamic response amplitudes with verbal and non-verbal memory scores.

2. Materials and methods

2.1. Subjects

We examined 21 right-handed TLE patients with unilateral HS including 12 LTLE patients (7 females, mean age 36.6 years, SD = 12.42, range 18–57) and 9 RTLE patients (2 females, mean age 52.2 years, SD = 13.77, range 21–70), who underwent presurgical evaluation at the University Hospital Tübingen. All patients had clear signs of hippocampal sclerosis on 3T structural MRI, including unilateral hippocampal atrophy and increased T2 signal intensity, as determined by experienced neuroradiologists. Further details regarding patient characteristics can be found in Table 1.

Furthermore, we included 28 healthy participants (21 female, mean age 28 years, SD = 6.17, range 18–46). All patients and healthy controls were native speakers of German and strongly right-handed (mean handedness quotient >0.97 in the group of healthy subjects as well as both patient groups) as assessed by the Edinburgh Inventory (Oldfield, 1971).

The study was approved by the Ethics committee of the University of Tübingen and was in accordance with the guidelines of the Declaration of Helsinki. All participants gave written informed consent.

2.2. Neuropsychological memory tests

To assess verbal learning and memory, we used a wordlist learning and memory test which required to memorize a list of 15 words (Verbaler Lern- und Merkfähigkeitstest, VLMT, (Helmstaedter and Durwen, 1990; Helmstaedter et al., 2000)). We assessed the 'immediate recall' memory score, i.e. the sum of words correctly reproduced during the five learning trials (max. 75).

Non-verbal learning and memory were evaluated using a revised version of the DCS (Diagnostikum für Cerebralschädigung (Lamberti and Weidlich, 1999)) during which subjects had to learn 9 geometrical figures. We assessed again the 'immediate recall' score, i.e. the sum of correctly reproduced figures during the five learning trials (max. 45).

As memory performance levels decrease with age (Jenkins et al., 2000; Park et al., 2002), we employed the standardized memory performance as compared to an age-matched reference population in the form of percentile ranks instead of absolute values (i.e. raw scores).

Furthermore, we assessed the level of verbal crystallized intelligence in each participant using the German multiple choice vocabulary test (MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl, 2005; Spreen and Strauss, 1998)), which has been shown to correlate with the Full Scale IQ of the HAWIE-R (Satzger et al., 2002).

2.3. Magnetic resonance data acquisition

MRI studies were performed on a Siemens Magnetom Sonata [Maestro Class] 1.5 T Scanner (Siemens AG, Erlangen, Germany). All data were acquired using an 8-channel array head coil for reception and the body coil for transmission. In order to obtain a high-resolution anatomical image of each subject's brain, a sagittal T1-weighted 3D–MPRAGE sequence was used (TR/TI/TE = 1300/660/3.19 ms, flip angle 15°, field of view = 256 ∗ 256 mm^2, matrix = 256 ∗ 256, 176 slices, voxel size = 1 ∗ 1 ∗ 1 mm^3). Additionally, a field map was recorded for distortion correction of the functional images caused by magnetic field inhomogeneity. For the fMRI task, 175 gradient-echo planar T2*-weighted images covering the whole brain were acquired (TR = 4000 ms, TE = 64 ms, field of view = 192 ∗ 192 mm^2, matrix = 64 ∗ 64, voxel size = 3 ∗ 3 ∗ 3 mm^3, gap = 0.3 mm, 38 interleaved slices). The first two images of each experimental run were discarded in order to reach equilibrium of magnetization.

2.4. Stimuli and fMRI task design

The stimuli were visually projected on a translucent screen positioned at the end of the scanner table using a video projector outside the magnet. Subjects saw the presentation via a mirror attached to the head coil. Outside the scanner room, a Windows Laptop using the software 'Presentation 0.6' (http://www.neurobehaviouralsystems.com) was connected to the video projector. Participants conveyed their responses via use of a two button box with their right thumb.

To investigate verbal and non-verbal memory functions, we used a face-name association paradigm, which comprised six encoding blocks. Each block consisted of four face-name pairs with simultaneous presentation of the face-name pair and a presentation duration of 7 s per each pair (plus 1 s black screen), and subjects were explicitly asked to memorize them (Fig. 1). This alternated with the control condition in which two scrambled versions of the previously shown faces were presented (Conway et al., 2008), and subjects had to indicate by button press whether the two pictures were identical or not (Fig. 1). This required response was implemented to ensure the participant's attention and cooperation.

Table 1
Demographic data of patients (N = 21).

Patients	Side of epilepsy	Age/sex	Age at seizure onset (years)	Duration of epilepsy (years)	Seizure frequency (seizures/month)	AEDs
Left HS group						
1	LTLE	30/F	15	15	8	LEV, LTG
2	LTLE	36/M	14	22	6	LCM, LEV
3	LTLE	47/M	19	28	2	LEV, RTG
4	LTLE	57/F	22	35	20	LEV
5	LTLE	46/M	37	9	20	LEV, OXC, RTG
6	LTLE	49/F	1	48	20	CBZ, CZP, LEV
7	LTLE	36/F	12	24	5	LCM, LEV, LTG, TPM
8	LTLE	46/M	17	29	12	LCM, LTG
9	LTLE	25/F	15	10	5	LTG
10	LTLE	28/F	19	9	4	LCM, LEV, LTG
11	LTLE	21/M	11	10	2	OXC
12	LTLE	18/F	13	5	0.25	VPA
Mean (SD)		36.58 (12.42)	16.25 (8.40)	20.33 (13.02)	10.75 (8.29)	
Right HS group						
1	RTLE	53/M	0	53	20	CBZ, LEV
2	RTLE	70/F	5	65	12	LCM, LEV
3	RTLE	51/M	48	3	0.33	ESL, LEV
4	RTLE	64/M	4	60	1	LTG, VPA, ZNS
5	RTLE	57/F	45	12	13	LCM, LEV
6	RTLE	51/M	10	41	30	CBZ, LCM, PB, RTG
7	RTLE	21/M	5	16	28	VPA
8	RTLE	57/M	43	14	3	LTG
9	RTLE	46/M	3	43	1	LCM, PER
Mean (SD)		52.22 (13.77)	18.11 (20.62)	34.11 (23.18)	15.67 (12.69)	

AEDs: antiepileptic drugs; HS: hippocampal sclerosis; LTLE: left temporal lobe epilepsy; RTLE: right temporal lobe epilepsy; F: female; M: male; LEV: levetiracetam; LTG: lamotrigine; LCM: lacosamide; RTG: retigabine; OXC: oxcarbazepine; CBZ: carbamazepine; CZP: clonazepam; TPM: topiramate; VPA: valproate; ESL: eslicarbazepine acetate; ZNS: zonisamide; PB: phenobarbital; PER: perampanel.

A recognition task was performed inside the scanner to ensure the participants' attention and compliance during the encoding condition (Fig. 1). It was designed as a two-alternative forced choice test, in which the 24 faces were shown with the correct and a false name printed underneath and subjects had to indicate by button press which name was the one previously associated with the face. The positions of correct names (left or right) were counterbalanced across items. The distractor name had also been shown during encoding but had been associated with a different face, to avoid that participants base their decision on familiarity alone. The items were presented in randomized order. The recognition task also included six activation blocks alternating with the control condition.

2.5. Image processing and fMRI data analysis

Imaging data were analyzed in MATLAB (http://www.mathworks.com) using Statistical Parametric Mapping (SPM 8, Wellcome Trust Centre for Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm). The imaging time series of each subject was corrected for difference in slice acquisition time, realigned and unwarped based on the estimated field map data (Andersson et al., 2001), co-registered to the anatomical reference image, and normalized to MNI space (Montreal Neurologic Institute Atlas) (Mazziotta et al., 1995). The normalized data were smoothed with an isotropic Gaussian kernel (8 mm full-width at half maximum) and filtered with a high pass filter with a cut-off time of 128 s.
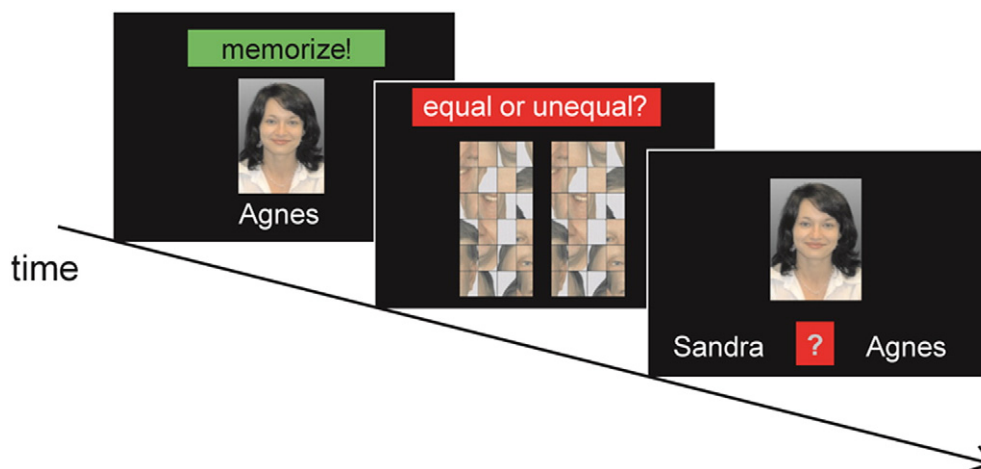

Fig. 1. Behavioural fMRI task: Participants were scanned while encoding and recognizing face-name associations. The encoding condition comprised six encoding blocks consisting of four face-name pairs and subjects were asked to memorize them. This alternated with the control condition in which two scrambled versions of the previously shown faces were presented, and subjects had to indicate by button press whether the two pictures were identical or not. The recognition task was designed as a two-alternative forced choice test in which the 24 faces were shown with the correct and a false name printed underneath and subjects had to indicate by button press which name was the one previously associated with the face.

For first level analyses, experimental task and control blocks were convolved with the hemodynamic response function in order to evaluate individual main effects for the encoding vs. control condition and realignment parameters were added as regressors of no interest.

In order to examine task-related group main effects, second level analyses using one-sample t-tests were performed in the group of healthy subjects. Results are reported at a height threshold of $p < 0.001$, uncorrected. Correction for multiple comparisons ($p < 0.05$, corrected) across the whole brain was assessed at cluster level using random field theory and only clusters exceeding an extent threshold of k > 60 voxels were considered for further analysis. Regions of interest (ROIs) were defined and masks created based on the activated clusters in the second-level analysis of the healthy subjects. These masks were then applied to the first-level results of each participant to extract activations, i.e. beta estimates, within each of the above defined ROIs to use for further analyses.

2.6. Behavioural data analyses and correlation analyses between fMRI and behavioural data

Data were analyzed using SPSS (statistical package for social sciences) version 22 for Windows (http://www.spss.com). Descriptive statistics were used to analyse sociodemographic and neuropsychological characteristics using minimum, maximum, mean and standard deviations (SD) for parametric data. To test for normal distribution, we used Kolmogorov-Smirnov tests. We calculated the percentages of correct answers for the fMRI control task. Differences between the behavioural performances of the three groups of participants were evaluated using the Kruskal-Wallis Test and specified afterwards by pairwise comparisons with adjusted p-values.

We compared activations between groups using the extracted fMRI activations from each ROI in each participant using two-sample t-tests. To remove variance correlated with participants' age, we performed a simple regression analysis with age as an independent variable and event-related responses in each ROI as dependent variables. Regression residuals obtained from this analysis were subsequently correlated with verbal and non-verbal memory scores. Correlation analyses were performed across all groups. It should further be noted that we only used activations within our predefined ROIs for correlation analyses to examine the characteristics of activations solely within areas relevant to our task. The significance level was set at $p < 0.05$.

3. Results

3.1. Neuropsychological memory performance

The neuropsychological data of LTLE and RTLE patients as well as the healthy subjects are presented in Table 2. Kolmogorov-Smirnov tests revealed for the healthy subjects non-normal distributions for IQ and VLMT (each $p < 0.05$) and normal distributions for the DCS ($p > 0.05$). For the LTLE patients, Kolmogorov-Smirnov tests revealed normal distributions for IQ ($p > 0.05$) and non-normal distributions for VLMT and DCS (each $p < 0.05$). RTLE patients showed non-normal distributions for IQ ($p < 0.05$) and normal distributions for VLMT and DCS (each $p > 0.05$).

Kruskal-Wallis tests revealed significant differences in IQ between LTLE patients and healthy subjects ($z = -4.204$, $p < 0.001$) as well as RTLE patients and healthy subjects ($z = -2.557$, $p = 0.032$), confirming once again that hippocampal damage affects cognitive functions negatively (French et al., 1993; Helmstaedter, 2002). However, no significant differences were seen between both patient groups ($p > 0.05$). Significant differences between LTLE patients and healthy subjects as well as RTLE patients and healthy subjects were also observable for the VLMT (LTLE vs. healthy: $z = -4.310$, $p < 0.001$; RTLE vs. healthy: $z = -2.774$, $p = 0.017$) score and the DCS score (LTLE vs. healthy: $z = -2.637$, $p = 0.025$; RTLE vs. healthy: $z = -2.581$, $p = 0.030$)

Table 2
IQ and memory performance in healthy subjects, LTLE and RTLE patients.

Group and variables	Minimum	Maximum	Mean (SD)
Healthy subjects ($n = 28$)			
IQ (MWT-B)	90.0	145.0	121.3 (16.7)
VLMT PR	5.0	100.0	75.0 (27.3)
DCS PR	12.3	100.0	71.2 (21.9)
LTLE ($n = 12$)			
IQ (MWT-B)	79.0	118.0	94.1 (11.2)
VLMT PR	0.0	85.0	20.0 (28.8)
DCS PR	5.0	92.0	37.2 (34.8)
RTLE ($n = 9$)			
IQ (MWT-B)	89.0	136.0	104.1 (17.1)
VLMT PR	0.0	90.0	34.4 (26.2)
DCS PR	0.0	81.5	37.1 (37.2)

LTLE: left temporal lobe epilepsy; RTLE: right temporal lobe epilepsy; MWT-B: Mehrfachwahl-Wortschatz-Intelligenztest (German multiple choice vocabulary test); VLMT: Verbaler Lern- und Merkfähigkeitstest (wordlist learning and memory test); DCS: Diagnostikum für Cerebralschädigung; PR: percentile ranks.

with no significant differences for all these scores between both patients groups (each $p > 0.05$).

3.2. fMRI behavioural data

Percent correct recognition performance showed 68.0 ± 18.1 correctly recognized face-name pairs in the LTLE group, 63.8 ± 19.0 in the RTLE group and 91.5 ± 5.7 in the group of healthy subjects. Kruskal-Wallis tests revealed significant differences between performances of LTLE patients and healthy subjects ($z = -3.989$, $p < 0.001$) as well as RTLE patients and healthy subjects ($z = -4.872$, $p < 0.001$), but no significant differences between performances of both patient groups ($p > 0.05$). Performance in the fMRI recognition task correlated linearly with VLMT ($R^2 = 0.537$, $p < 0.001$) and DCS ($R^2 = 0.361$, $p < 0.001$) scores, underlining the ability of this task to map verbal and non-verbal memory functions.

In the control condition the rate of correct responses was 93.1 ± 9.3 for the LTLE group, 79.0 ± 37.2 for the RTLE group and 98.3 ± 4.3 for the healthy participants, demonstrating that our subjects attended to the task.

3.3. fMRI analyses

3.3.1. Second-level analyses – ROI definition

In healthy participants, the contrast between encoding and control blocks revealed activations in bilateral hippocampus (HC), left inferior frontal gyrus (IFG), left superior frontal gyrus (SFG), left superior temporal gyrus (STG), bilateral angular gyrus (AG), bilateral medial prefrontal gyrus (MPFG) and right anterior temporal lobe (ATL) (for further details see Table 3). These clusters were defined as ROIs for further analyses. The fMRI activations for each ROI and participants' group are shown in Table 4.

Table 3
Brain regions activated during face-name encoding task in the group of healthy subjects ($N = 28$).

Brain regions	MNI coordinates	Z score[*]	Cluster size
Bilateral medial prefrontal gyrus	−3 42 −15	6.93	317
Left inferior frontal gyrus	−45 33 −12	5.90	364
Left angular gyrus	−57 −66 24	5.74	354
Left superior temporal gyrus	−51 −21 −12	5.60	256
Right hippocampus	30 −18 −15	5.56	78
Left superior frontal gyrus	−21 27 57	5.36	487
Left hippocampus	−21 −15 −15	5.28	76
Right angular gyrus	51 −66 39	5.07	73
Right anterior temporal lobe	60 −9 −21	4.04	62

[*] $p < 0.05$, correct at cluster level (k > 60 voxels).

3.3.2. Comparison of activations between groups

Comparing activations within each ROI between groups revealed that LTLE patients activated significantly less than healthy controls in the left HC ($t = -2.219$, $p = 0.044$) (Fig. 2), as hypothesized. Regarding the above defined ROIs, we were able to identify further brain regions showing different activation patterns than healthy subjects: LTLE patients activated significantly less in the left SFG ($t = -2.767$, $p = 0.009$) (Fig. 3), the left IFG and the left STG. However, the latter two did not remain significant after correcting the fMRI activations for age as described above. In RTLE patients, we were also able to confirm our first hypothesis: as predicted, they activated significantly less in the right HC than healthy controls ($t = -4.367$, $p < 0.001$), but also in the left HC ($t = -3.316$, $p = 0.002$) (Fig. 2). Further regions showing less activation were the left SFG ($t = -3.074$, $p = 0.004$) (Fig. 3) and the right AG ($t = -3.290$, $p = 0.002$) (Fig. 3). Activations in all other ROIs did not differ significantly between groups (each $p > 0.05$).

3.4. Correlation analyses

Correlation analyses between fMRI activations and verbal and non-verbal memory scores across all groups yielded significant linear correlations between activations in the left HC and VLMT scores ($R^2 = 0.419$, $p < 0.001$) (Fig. 2). Furthermore, we observed significant linear correlations between VLMT scores and activations in the right HC ($R^2 = 0.176$, $p < 0.01$) (Fig. 2), the left SFG ($R^2 = 0.244$, $p < 0.001$) (Fig. 3) and the right ATL ($R^2 = 0.084$, $p < 0.05$) (Fig. 3). The DCS score showed significant linear correlations with activations in the left HC ($R^2 = 0.184$, $p < 0.01$) (Fig. 2), the right HC ($R^2 = 0.166$, $p < 0.01$) (Fig. 2) and the left SFG ($R^2 = 0.181$, $p < 0.01$) (Fig. 3). Activations in all other ROIs did not reveal any significant correlations with memory scores (each $p > 0.05$).

Unsurprisingly, correlation analyses between fMRI activations and fMRI behavioural data revealed very similar results: we observed significant linear correlations with activations in the left HC ($R^2 = 0.378$, $p < 0.001$), the right HC ($R^2 = 0.234$, $p < 0.01$) and the left SFG ($R^2 = 0.252$, $p < 0.01$). All other ROIs did not yield any significant linear correlations with fMRI behavioural data (each $p > 0.05$).

4. Discussion

The aim of the current study was to investigate verbal and non-verbal memory networks in left and right TLE patients compared to healthy adults using a face-name association task.

In agreement with our hypothesis, LTLE patients activated significantly less in the left HC than healthy controls, whereas RTLE patients showed significantly less activations in the right HC. Correlation analyses revealed significant correlations between the verbal memory scores and activations in the left, but also – with less explained variance – the right HC, as well as the left SFG and right ATL, indicating involvement of

Table 4
fMRI activations (beta estimates) in healthy subjects, LTLE and RTLE patients in each ROI.

ROI	Group mean (SD)		
	Healthy subjects	LTLE	RTLE
Left HC	0.37 (±0.31)	0.08 (±0.51)	0.24 (±0.21)
Right HC	0.34 (±0.26)	0.33 (±0.34)	0.06 (±0.27)
Left IFG	0.52 (±0.36)	0.12 (±0.54)	0.36 (±0.20)
Left SFG	0.54 (±0.36)	0.20 (±0.45)	0.22 (±0.28)
Left STG	0.33 (±0.22)	0.16 (±0.21)	0.35 (±0.24)
Left AG	0.85 (±0.58)	0.75 (±0.51)	0.54 (±0.45)
Right AG	0.69 (±0.63)	0.52 (±0.52)	0.09 (±0.68)
MPFC	0.66 (±0.45)	0.72 (±0.40)	0.61 (±0.29)
Right ATL	0.36 (±0.37)	0.29 (±0.37)	0.22 (±0.33)

ROI: region of interest; HC: hippocampus; IFG: inferior frontal gyrus; SFG: superior frontal gyrus; STG: superior temporal gyrus; AG: angular gyrus; MPFC: medial prefrontal cortex; ATL: anterior temporal lobe; LTLE: left temporal lobe epilepsy patients; RTLE: right temporal lobe epilepsy patients; SD: standard deviations.
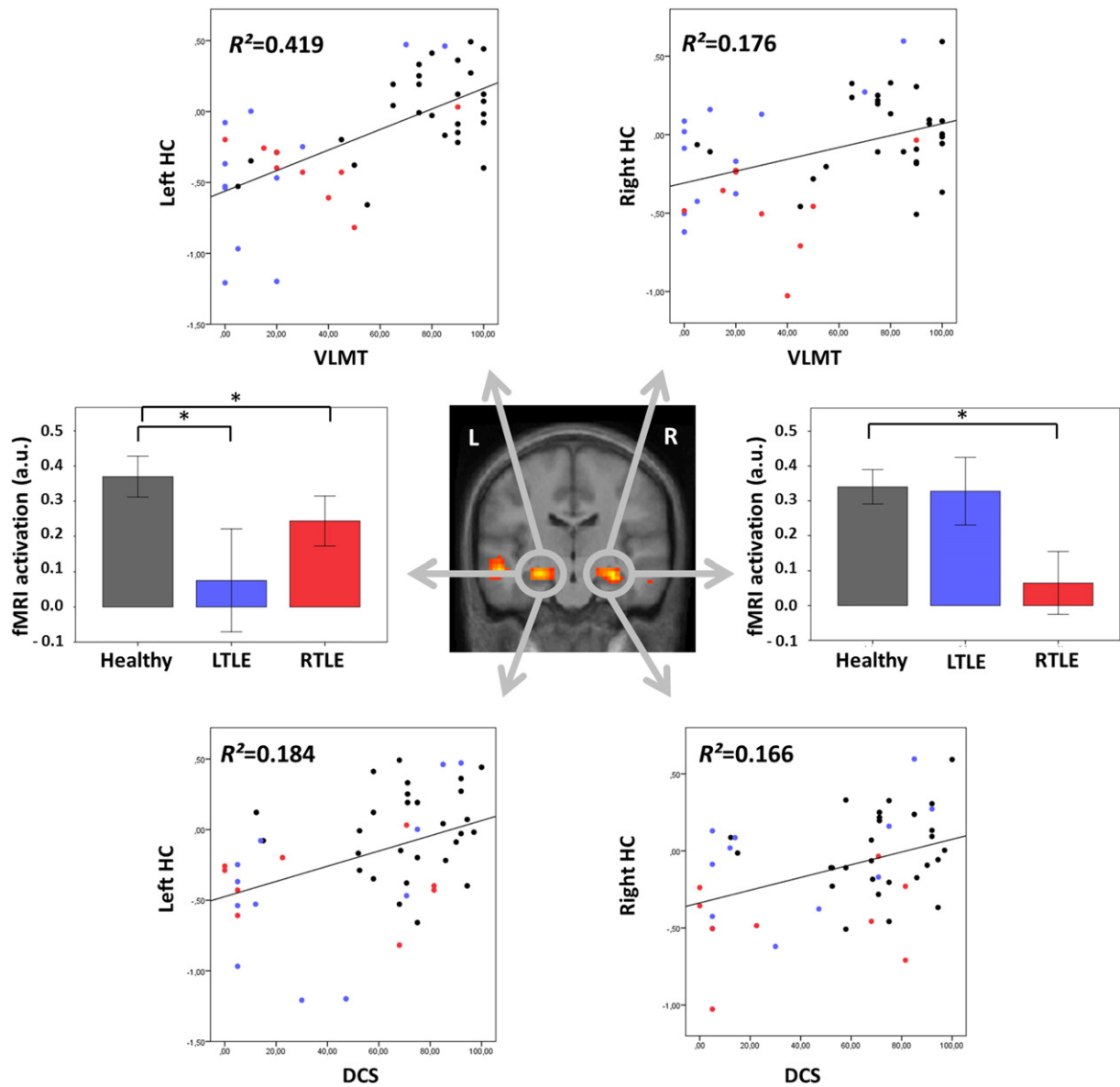
these regions in the verbal memory system. The non-verbal memory system seems to receive contributions from both HC and the left SFG, as activations in these regions correlated significantly with non-verbal memory scores. We were also able to demonstrate altered activations in TLE patients as compared to healthy subjects in brain areas involved in face-name encoding: LTLE patients activated significantly less in the left HC and the left SFG. RTLE patients, on the other hand, showed less activations in both HC as well as the right AG, but also, similarly as LTLE patients, in the left SFG.

4.1. Validity of a face-name association task in investigating both verbal and non-verbal memory functions

As already described in our previous study, the face-name association task elicited robust bilateral mesial temporal activations in healthy subjects (Klamer et al., 2013), which is in accordance with existing literature (Kirwan and Stark, 2004; Sperling et al., 2003). In line with the current theory on dynamic interactions between left and right mesial temporal regions in verbal and non-verbal memory processes (Saling, 2009), we demonstrated significant correlations of activations within the left HC and to a lesser degree within the right HC with verbal memory scores and activations within both HC with non-verbal memory scores. These correlations indicate the applicability of this face-name paradigm for investigating memory functions in both left and right TLE patients. This would enable the investigator to perform only one single fMRI paradigm that addresses both memory functions instead of two material-specific memory fMRI paradigms, which has the advantage of being faster and easier to apply in everyday clinical routine and thus represents an additional gain in the presurgical evaluation of TLE patients. However, a clear differentiation between both memory systems, i.e. verbal and non-verbal, is not possible with this paradigm alone. To assess reorganization processes restricted to one memory system only, one would have to apply material-specific tasks.

In addition, this paradigm could be used to quantify memory functions and differentiate between subjects with good and those with bad or impaired memory, which is often the case in TLE patients, as activation correlated linearly with memory performance, i.e. subjects with good memory performance in neuropsychological tests demonstrated high activations and subjects, mainly TLE patients, who performed poorly in neuropsychological memory tests showed lower activations.

Whole brain activations in healthy subjects further include the left and right angular gyrus and the bilateral ventromedial prefrontal cortex, i.e. areas belonging to the so called default mode network (DMN). This network is usually deactivated during cognitive tasks, but has also been associated with episodic memory functions. In fact, several fMRI studies have suggested that memory functions are subserved not only by mTL structures but also by distinct cortical areas belonging to the DMN (for review see (Jeong et al., 2015)).

4.2. Alterations in memory processing networks in LTLE patients

LTLE patients activated significantly less in the left HC than healthy controls and patients with RTLE. This hypoactivation comes along with left-sided hippocampal pathology, suggesting relevant contribution of the latter to memory performance. It is further accompanied by verbal memory deficits, as fMRI activations in the left HC show significant positive linear correlations with verbal memory scores. Using material-specific tasks, this has been reported previously. Bonelli et al. (2010) observed linear correlations between left hippocampal activation and verbal memory in LTLE patients using a word encoding paradigm. This concordance with existing literature on material-specific tasks underlines the ability of our "combined" paradigm to investigate verbal and non-verbal memory functions equally. In fact, with an explained variance of 42%, the ability of our face-name task to reflect verbal memory functions via fMRI is rather high. However, we also observed, though to a lesser extent, correlations of activation within the left HC with

Fig. 2. fMRI activations in left and right HC in healthy subjects during encoding of face-name pairs. Bar graphs demonstrate activations in both ROIs in all three groups. In the left HC, LTLE and RTLE patients activate significantly less than healthy controls. In the right HC, RTLE patients show significantly lower activations than healthy controls. Scatterplots demonstrate correlation analyses between activations and memory scores, the black dots represent healthy controls, blue dots LTLE patients and red dots RTLE patients. Correlation analyses revealed linear correlations between verbal memory scores and activations in the left, but also the right HC, and additionally between non-verbal memory scores and activations in the right HC as well as the left HC.

non-verbal memory scores. This indicates, that the left HC is not strictly confined to verbal memory but does also mediate non-verbal memory functions and might even be involved in associative memory, i.e. binding together verbal and non-verbal information. In fact, there is evidence for the integration of distributed information into episodic memory representations within the hippocampus (Backus et al., 2016).

As opposed to several other studies, we did not observe any compensatory activation in the contralateral mesial temporal lobe. LTLE patients demonstrated equally strong activations as healthy controls with no hyperactivations observable. However, we observed linear correlations between activations in the contralateral, i.e. the right, hippocampus with verbal memory scores, indicating that this structure also contributes to verbal memory functions, although to a lesser extent, as the explained variance of 18% remained clearly below that of the left HC. This finding is in line with the hippocampal reserve theory with partial maintenance of verbal memory functions in the contralesional hippocampus (Chelune et al., 1991). The functional adequacy model,

on the other hand, suggests that it is the functional capacity of the ipsilesional hippocampus that maintains memory functions (Chelune et al., 1991). The literature provides support for both theories (Bonelli et al., 2013; Cheung et al., 2009). Our data indicate that both hippocampi seem to be involved in verbal memory functions with the left being the dominant one.

Differences between healthy subjects and LTLE patients were not only observed in the hippocampal ROI. The left SFG, i.e. the left dorsolateral prefrontal cortex, is associated with attention, working memory and executive functions critical for memory processes (Alessio et al., 2013; Burgess et al., 2001). Further, this region is associated with monitoring of behaviour and strategic processing, but has also been described to play an important role in encoding and retrieval of episodic memory in healthy subjects with greater activation being positively correlated with better memory performance (Grady et al., 2003; Kelley et al., 1998; Menon et al., 2005). This is in accordance with our results, as activity in this region correlated positively with verbal as well as non-
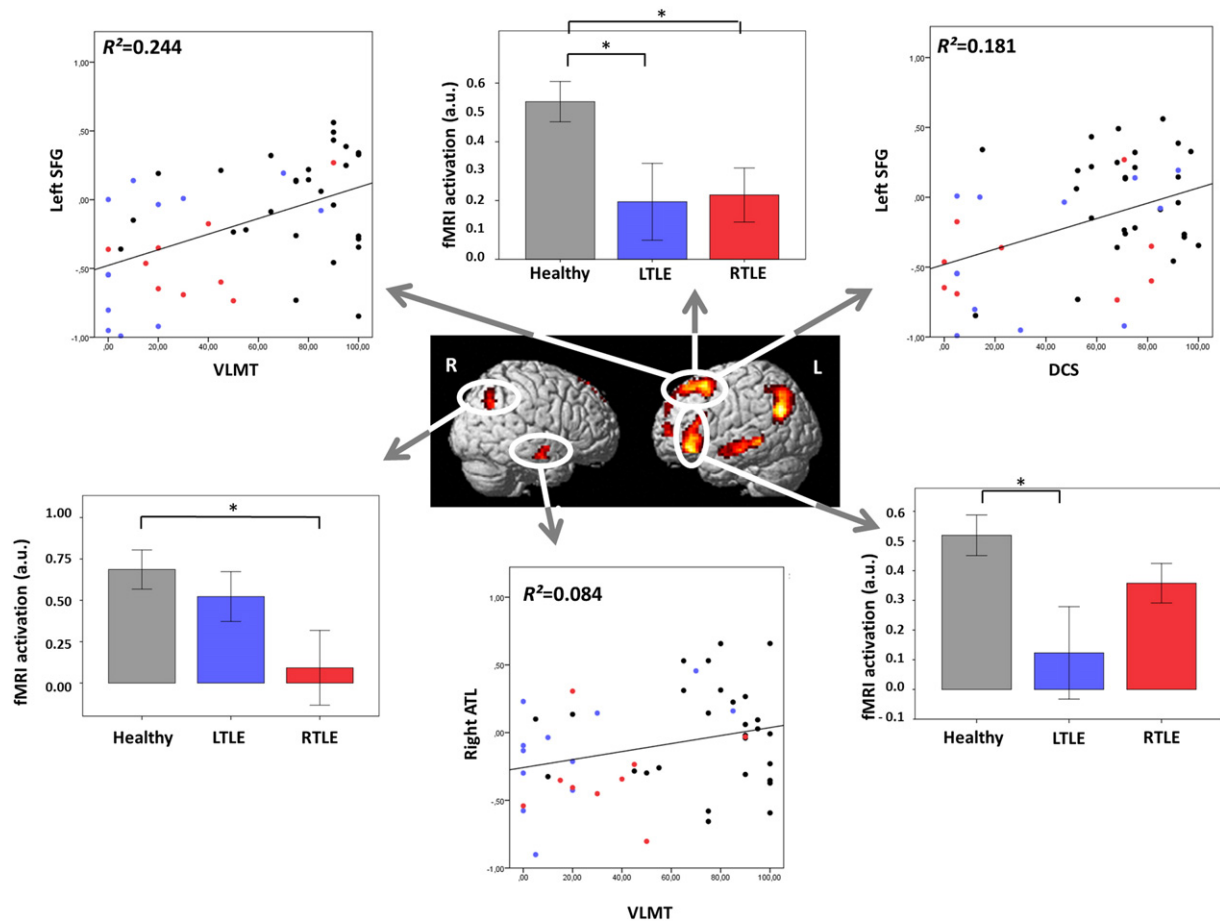
Fig. 3. fMRI activations in the left SFG and IFG and the right AG and ATL in healthy subjects during encoding of face-name pairs. Bar graphs demonstrate activations in all three groups. In the SFG, both LTLE and RTLE patients activate significantly less than healthy controls. In the IFG, LTLE patients activate significantly less than healthy controls. In the right AG, RTLE patients activate significantly less than healthy controls. Scatterplots demonstrate correlation analyses between activations and memory scores, the black dots represent healthy controls, blue dots LTLE patients and red dots RTLE patients. Verbal memory scores are linearly correlated with fMRI activations in the left SFG and the right ATL. Non-verbal memory scores show significant correlations with fMRI activations in the left SFG.

verbal memory scores. This extends recently reported findings, as this region seems to mediate verbal and visual-spatial memory processes equally and does not demonstrate material-specificity regarding the stimuli encoded. In line with this goes the observation that left and right TLE patients showed less activity in this ROI than our healthy controls.

4.3. Alterations in memory processing networks in RTLE patients

Analogous to the LTLE patients, RTLE patients activated significantly less in the right, i.e. the ipsilateral lesioned hippocampus, but also in the contralateral hippocampus than healthy controls. Activations in both hippocampi showed significant linear correlations with non-verbal memory scores with very similar explained variances (17% in the right and 18% in the left HC) underlining that the non-verbal memory system seems to have a more bilateral representation in the brain (Bonelli et al., 2013; Helmstaedter and Kurthen, 2001). One reason for this might be that visual-spatial material can also be memorized using verbal encoding strategies (Bonelli et al., 2013). Regarding reorganization processes in RTLE patients, Banks et al. (2012) reported reorganization of non-verbal memory functions to the left HC, but also more recruitment from the right, i.e. ipsilateral, parahippocampal and hippocampal cortices, compared to healthy controls. However, in contrast to this observation, our RTLE patients showed reduced rather than increased activations in both HC. Further, we did not observe any additional temporal activations in RTLE patients compared to healthy controls as

opposed to Sidhu et al. (2013), who observed in RTLE patients increased temporal activations within the superior temporal gyri bilaterally.

RTLE patients showed also less activity in the right angular gyrus which is in line with results associating this area with episodic memory encoding and retrieval (Spaniol et al., 2009). Furthermore, several neuroimaging studies have suggested involvement of the angular gyrus in attention mechanisms. Especially the right angular gyrus has been suggested to be involved in visual-spatial attention (Seghier, 2013). In accordance with these findings, our results suggest involvement of the right angular gyrus in non-verbal, i.e. visual-spatial, memory networks. If these networks are disturbed, as is the case in RTLE patients with right hippocampal sclerosis, activation in this region decreases.

Another rather surprising finding in the RTLE group was the lower rate of correct responses in the control task. This might indicate that these patients attended less to the stimuli. However, during the recognition task there were no significant differences between both patient groups which corresponds to the neuropsychological memory data also showing no significant differences between both patient groups regarding IQ, VLMT, and DCS scores. A possible reason for this lower performance of RTLE patients in the control task might be difficulties with the control task itself (e.g. altered visuospatial processing).

4.4. Strengths and limitations of the study

While our face-name association paradigm offered to investigate verbal and non-verbal memory functions within one experiment, this

procedure has the disadvantage that a clear differentiation between the two memory systems is not possible. Therefore, assessment of reorganization processes which are restricted to one memory system would require application of material-specific tasks.

Hippocampal sclerosis is a rare condition explaining the rather small sample sizes of LTLE and RTLE patients in the current study which prevented application of meaningful comparisons between groups on a whole-brain level due to the ensuing multiple comparison problem. Therefore, we restricted our analyses to brain areas which were identified in a large group of healthy subjects as neural correlates underlying encoding of face-name pairs. While this procedure clearly enhanced the sensitivity of our approach, it has the drawback of being blind for alterations outside the identified network for face-name encoding in healthy subjects.

One of the most frequently applied analysis methods in memory research is contrasting correctly remembered trials with later forgotten ones (Bonelli et al., 2010; Friston et al., 1998; Richardson et al., 2004). However, this type of analysis is not feasible with our data for two reasons: First, the primary aim of the experimental design was to ensure a level of difficulty that could still be managed by TLE patients exhibiting moderate to severe memory deficits. As a consequence, we obtained a high rate of correct responses in the group of healthy subjects ($91.5 \pm 5.7\%$) and even some of the patients. Thus, a statistical comparison of remembered versus forgotten items is severely underpowered due to the low number of forgotten items in many study participants. Second, we employed a block design prohibiting to clearly disentangle neural responses to single trials.

5. Conclusions

Our results demonstrate that the face-name association task can be employed to examine functional alterations during encoding of both verbal and non-verbal stimuli in one fMRI paradigm. In line with our predictions, diminished activation within the hippocampus was found depending on the side of hippocampal sclerosis. Correlation of activation and performance in standard clinical tests for the assessment of verbal and non-verbal memory underscores the clinical relevance of these changes. Moreover, changes in activation were also noted in the left SFG in both patient groups. Activity in this area correlated with memory performance in verbal and non-verbal tasks suggesting this area as a convergence region for the encoding of verbal and nonverbal material.

Disclosure of conflicts of interest

None of the authors has any conflict of interest to disclose.

Acknowledgments

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