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Lesion side matters — An fMRI study on the association between neural correlates of watching dynamic fearful faces and their evaluation in patients with temporal lobe epilepsy

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ABSTRACT

Most studies assessing facial affect recognition in patients with TLE reported emotional disturbances in patients with TLE. Results from the few fMRI studies assessing neural correlates of affective face processing in patients with TLE are divergent. Some, but not all, found asymmetrical mesiotemporal activations, i.e., stronger activations within the hemisphere contralateral to seizure onset. Little is known about the association between neural correlates of affect processing and subjective evaluation of the stimuli presented. Therefore, we investigated the neural correlates of processing dynamic fearful faces in 37 patients with mesial temporal lobe epilepsy (TLE; 18 with left-sided TLE (lTLE), 19 with right-sided TLE (rTLE)) and 20 healthy subjects. We additionally assessed individual ratings of the fear intensity and arousal perception of the fMRI stimuli and correlated these data with the activations induced by the fearful face paradigm and activation lateralization within the mesiotemporal structures (in terms of individual lateralization indices, LIs). In healthy subjects, whole-brain analysis showed bilateral activations within a widespread network of mesial and lateral temporal, occipital, and frontal areas. The patient groups activated different parts of this network. In patients with lTLE, we found predominantly right-sided activations within the mesial and lateral temporal cortices and the superior frontal gyrus. In patients with rTLE, we observed bilateral activations in the posterior regions of the lateral temporal lobe and within the occipital cortex. Mesiotemporal region-of-interest analysis showed bilateral symmetric activations associated with watching fearful faces in healthy subjects. According to the region of interest and LI analyses, in the patients with lTLE, mesiotemporal activations were lateralized to the right hemisphere. In the patients with rTLE, we found left-sided mesiotemporal activations. In patients with lTLE, fear ratings were comparable to those of healthy subjects and were correlated with relatively stronger activations in the right compared to the left amygdala. Patients with rTLE showed significantly reduced fear ratings compared to healthy subjects, and we did not find associations with amygdala lateralization. Although we found stronger activations within the contralateral mesial temporal lobe in the majority of all patients, our results suggest that only in the event of left-sided mesiotemporal damage is the right mesial temporal lobe able to preserve intact facial fear recognition. In the event of right-sided mesiotemporal damage, fear recognition is disturbed. This underlines the hypothesis that the right amygdala is biologically predisposed to processing fear, and its function cannot be fully compensated in the event of right-sided mesiotemporal damage.

1. Introduction

In the last decade, there have been a growing number of studies investigating affective processing in patients with mesial temporal lobe epilepsy (TLE). Deficits in affective processing are closely linked to damage in limbic brain areas, including the amygdala, a region that is frequently structurally and/or functionally affected in patients with mesial TLE [1,2]. In patients with TLE, structural damage of the amygdala is most likely associated with psychiatric abnormalities, such as aggression, dysthymia, or psychosis in patients with TLE [3–5]. Some experimental behavioral studies also assessed the consequences of mesiotemporal damage on affect processing in patients with TLE, most frequently by using tasks assessing facial affect recognition and evaluation. The results of those studies are not completely consistent, although most reported more pronounced emotion processing deficits in patients with right-sided TLE (rTLE) compared to patients with left-sided TLE (lTLE). For instance, Meletti et al. [6] reported reduced emotion expression recognition in patients with rTLE but did not find deficits in patients with lTLE (see also [7]). Sedda et al. [8] recently reported that patients with rTLE, but not patients with lTLE, are impaired in identifying negative emotions from faces, especially when faces were presented with low emotion expression intensity. However, Glogau et al. [9] found low performance in identifying and remembering emotional facial expressions in patients with lTLE but not in patients

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with rTLE. Bonora et al. [10] reported similar reductions in facial emotion and emotional prosody recognition in patients with rTLE and lTLE. In contrast, Fowler et al. [11] did not find emotion processing deficits in four different tasks (including a task with facial expressions) in patients with TLE compared to healthy subjects.

There are some functional imaging studies using emotional face paradigms to assess patterns of emotion-associated fMRI activations in patients with TLE. An fMRI study by Schacher et al. [12] suggested that activations of mesiotemporal brain structures (mainly the amygdala) induced by viewing dynamic fearful faces are lateralized in patients with TLE but not in healthy subjects (see also [13]). Stronger mesiotemporal activations were found in the nonepileptic mesial temporal lobe. Such asymmetrically lateralized activations were reported even on the individual level, i.e., 11 of 12 patients with mesial TLE had relatively stronger amygdala activations contralateral to the side of seizure onset. However, the results of Benuzzi et al. [14] suggest a lateralization of mesiotemporal activations towards the nonepileptic temporal lobe induced by viewing fearful static (versus neutral) faces only in patients with lTLE but not in patients with rTLE. In contrast with this result, Batut and colleagues [15] found significant activations within the left, but not the right, amygdala and parahippocampal gyrus (beyond a large network of bilateral frontal, temporal, and occipital activations) in patients with lTLE when viewing fearful compared to neutral faces. In patients with rTLE, they found a network of left-hemispheric activations including the left parahippocampal gyrus but not the amygdala. Bonelli et al. [16] reported no mesiotemporal activations in patients with lTLE but found bilateral mesiotemporal activations in patients with rTLE when viewing static fearful compared to neutral faces. Thus, findings of mesiotemporal activation patterns in TLE measured with fear-related fMRI tasks remain divergent. In addition, very little is known about the relationship between reductions in recognizing and/or evaluating affective stimuli and alterations of fMRI activations induced by affective stimuli in patients with TLE. In the above fMRI studies, the authors did not directly assess this association.

In the current study, we used the dynamic fearful face fMRI paradigm by Schacher et al. [12] in a larger sample of patients with left- and right-sided mesial TLE and healthy subjects. According to their results, we hypothesized relatively stronger mesiotemporal activations in the temporal lobe contralateral to the side of seizure onset within the two patient samples on the group level. To test this hypothesis in more detail, we calculated individual lateralization indices (LIs) within the amygdala and within a larger mesiotemporal region of interest (ROI) comprised of the hippocampus, the parahippocampal gyrus, and the amygdala. According to the majority of behavioral studies in patients with TLE reporting disturbances in facial affect processing, we further hypothesized that patients with TLE had lower fear intensity and arousal ratings when viewing fearful faces compared to healthy subjects. We also aimed to directly correlate subjective stimuli evaluation with fMRI activations and with the mesiotemporal LIs.

2. Methods

2.1. Patients

We investigated 18 patients with lTLE, 19 patients with rTLE, and 20 healthy subjects. Patients were recruited consecutively from the presurgical epilepsy workup program between September 2010 and June 2011. Exclusion criteria were focal epilepsy not of unilateral mesiotemporal origin, nonlesional mesial TLE, cognitive impairments impeding the fMRI investigation, and disagreement to participate in the fMRI study. All patients had unilateral mesiotemporal lesions proven with high-resolution structural MRI. Sociodemographic and epilepsy-related data are summarized in Table 1. Patients with lTLE and rTLE did not differ according to age at seizure onset ($p = .95$) and epilepsy duration ($p = .93$). A multivariate ANOVA with the dependent variables "age" and "years of school education" reflected no main effect for age ($F = .06$, $p = .95$). We found a main effect of years of school education ($F = 4.0$, $p = .03$), resulting from significantly higher school education of healthy subjects compared to patients with lTLE ($p = .02$) and patients with rTLE ($p = .01$).

Table 1
Sociodemographic and epilepsy-related data.

	Patients with lTLE (n = 18)	Patients with rTLE (n = 19)	Healthy subjects (n = 20)
Sex	9 females, 9 males	13 females, 6 males	13 females, 7 males
Age	m = 39.5 (SD = 12.42)	m = 38.79 (SD = 11.76)	m = 37.01 (SD = 9.9)
Education (school years)	m = 10.33 (SD = 1.94)	m = 10.28 (SD = 1.64)	m = 11.08 (SD = 1.52)
Age at onset	m = 16.94 (SD = 13.64)	m = 16.68 (SD = 10.86)	–
Epilepsy duration	m = 22.69 (SD = 17.5)	m = 21.22 (SD = 14.0)	–

The study protocol was in accordance with the Declaration of Helsinki and approved by the ethical committee of the University of Bielefeld. All subjects gave written informed consent prior to the investigation.

2.2. fMRI paradigm

We used the affective fMRI paradigm developed by Schacher et al. [12]. This blocked paradigm consists of eight activation blocks and eight resting blocks (each lasting 30 s). In the activation blocks, subjects watched 8–12 soundless scenes from thriller and horror movies showing faces expressing intense fear. The causes of fear reactions in terms of violence, aggressive harassment, or weapons were not shown. In the resting blocks, 8–12 dynamic landscape scenes were presented. Activation and resting blocks were shown alternately. Stimuli were presented via a laptop and projector on a translucent screen. Subjects with reduced visual acuity were provided with fMRI-suitable glasses to correct vision. Subjects were instructed to simply watch the film scenes.

2.3. Post-fMRI ratings

After the scanning procedure, a rating was conducted. Firstly, subjects were asked which emotion was expressed by the people seen during scanning (all subjects correctly identified fear). Then, we showed 24 of the presented fearful face scenes again. After each scene, the subjects rated how arousing they experienced the scene on a seven-point Likert scale (1 = not arousing at all, 7 = absolutely arousing). We also asked them how fearful each of the 24 persons appeared to them (1 = not fearful at all, 7 = absolutely fearful).

2.4. MR image acquisition and analyses

Structural and echo planar images (EPIs) were acquired on a 1.5-T magnetom symphony scanner (Siemens, Erlangen, Germany). Functional data were acquired using T2*-weighted sequences with the following parameters: 28 axial slices, 4-mm slice thickness, TR: 3000 ms, TE: 50 ms, 90° flip angle, FOV: 128 mm, matrix: 64 × 64 (voxel size: 3 × 3 × 4 mm). The EPIs were aligned to the AC–PC line. To allow for T1 saturation, the EPI sequence started with two dummy scans which were discarded directly. The original images were processed using SPM8. To correct for head movements, images were realigned using the SPM8 default algorithm. The realigned images were spatially normalized and resliced using the standard stereotactic space (MNI brain) to correct for individual anatomical differences. Then, spatial smoothing was applied with a Gaussian kernel of 8-mm FWHM to increase signal and anatomical conformity. Based on individual contrasts (activation condition > rest condition), a random effect analysis was conducted to reflect fear processing-associated fMRI activation. We conducted

one-sample t-tests for each group and two-sample t-tests for between-group analyses in the whole brain (thresholded at $p < .05$, FWE-corrected). We additionally conducted all analyses in a mesiotemporal ROI comprised of the hippocampus, the parahippocampal gyrus, and the amygdala according to predefined anatomical ROIs of the wfu pickatlas (Maldjian, http://www.nitrc.org/projects/wfu_pickatlas). ROI analyses were thresholded at $p<.001$, uncorrected. The wfu pickatlas was also used for anatomical labeling of the peak activations found. Subjective emotion ratings were used as regressors in a multiple regression analysis in order to correlate the subjective ratings with fear processing fMRI activity in these two ROIs.

In order to assess individual lateralization, we took activated voxels within the mesiotemporal ROI and within an amygdala ROI into account. The LIs have been calculated with an adaptive thresholding algorithm [17]. This adaptive thresholding algorithm was chosen because it provides robust calculations. LIs vary between −1 (completely right-lateralized) and +1 (completely left-lateralized).

3. Results

3.1. Behavioral data

To test the hypothesis of reduced fear and arousal ratings in patients with TLE, we calculated two univariate ANOVAs to analyze between-group differences in fear and arousal ratings (see Fig. 1). We did not find a significant main effect when analyzing between-group effects for arousal ratings ($F = 1.98$, $df = 2$, $p = .15$). We found a significant main effect "group" for fear intensity ratings ($F = 5.18$, $df = 2$, $p = .009$). Post hoc testing showed that patients with rTLE (mean = 4.00, SD = 0.86) had significantly lower fear ratings compared to the healthy subjects (mean = 5.02, SD = 0.86; $p = .01$). Patients with lTLE (mean = 4.69, SD = 1.15) did not differ significantly from the patients with rTLE ($p = .16$) and the healthy subjects ($p = .65$). We did not find significant correlations between the ratings and age, years of school education, age at epilepsy onset, as well as epilepsy duration (all $r \leq .31$, all $p \geq .30$).

3.2. fMRI data

3.2.1. Within-group results

The whole-brain results for each group (one-sample t-tests, thresholded at $p < .05$, FWE-corrected) are summarized in Table 2.

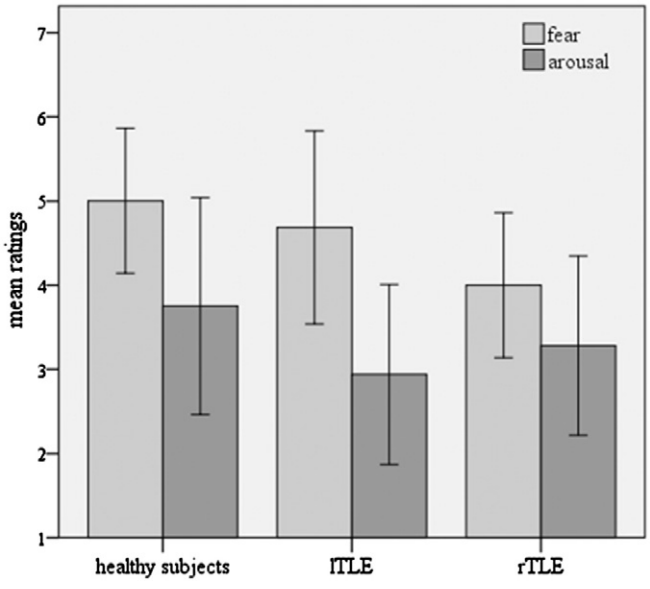

Fig. 1. Mean fear and arousal ratings of healthy subjects and patients (+/−SDs).

Mainly, healthy subjects had bilateral mesiotemporal, temporolateral, frontal, and occipital activations. In the patient groups, the whole-brain analyses reflected activations restricted to parts of the healthy subjects' network. The patients with lTLE had temporolateral activations within the right hemisphere and a cluster of left-sided superior frontal gyrus activation. The patients with rTLE had the activations within posterior brain regions of both hemispheres.

To test the hypothesis of stronger mesiotemporal activations contralateral to the side of seizure origin in patients with TLE, we first calculated one sample t-tests (activation > rest condition, thresholded at $p<.001$, uncorrected) within the mesiotemporal ROI for each of the three groups. Results are displayed in Figs. 2A–C. In a second step, we compared whether these activations significantly differed between groups (see results of the groupwise comparison in Section 3.2.2). The healthy subjects had symmetrical bilateral mesiotemporal activations (right amygdala, anterior hippocampus, parahippocampal gyrus: $x = 34$, $y = -12$, $z = -18$, $k = 561$, $z = 5.87$, $p<.001$; and left amygdala, anterior hippocampus, and parahippocampal gyrus: $x = -18$, $y = -12$, $z = -18$, $k = 424$, $z = 5.7$, $p < .001$). Patients with lTLE had stronger right-sided mesiotemporal activation (amygdala and anterior hippocampus: $x = 30$, $y = -2$, $z = -16$, $k = 77$, $z = 4.93$, $p<.001$) but also exhibited a cluster of significant activation within the left mesial temporal lobe (amygdala and anterior hippocampus: $x = -26$, $y = -14$, $z = -14$, $k = 44$, $z = 4.46$, $p < .001$). Patients with rTLE had left-sided mesiotemporal activations only (amygdala and anterior hippocampus: $x = -26$, $y = -8$, $z = -14$, $k = 35$, $z = 5.23$, $p = .04$). Overall, patients with rTLE showed the weakest activations (in the mesiotemporal ROI and within the whole brain).

3.2.2. Group comparisons

Within the whole-brain analyses, patients with lTLE compared to healthy subjects had stronger activations within the left frontal pole ($x = -6$, $y = 60$, $z = 28$, $k = 246$, $z = 4.17$, $p = .007$). The healthy subjects tended to have stronger left-sided mesiotemporal activations compared to the patients with lTLE; however, this was not a significant difference ($p = .08$).

Compared to patients with rTLE, the healthy subjects had stronger activations within a cluster comprised of the right hippocampus, parahippocampal gyrus, and the amygdala ($x = 18$, $y = -14$, $z = -20$, $k = 468$, $z = 4.76$, $p < .001$), a temporooccipital cluster ($x = 42$, $y = -60$, $z = -4$, $k = 434$, $z = 4.35$, $p < .001$), and a cluster on the left fusiform gyrus ($x = -30$, $y = -44$, $z = -20$, $k = 247$, $z = 4.20$, $p = .005$). In the inverted two-sample t-tests (patients with rTLE > healthy subjects), we found stronger activations within the occipital lobe (calcarine gyrus: $x = 0$, $y = -88$, $z = 4$, $k = 233$, $z = 4.0$, $p = .01$) in the patients with rTLE.

The ROI analyses reflected that healthy subjects, compared to patients with lTLE, had significantly more activation within the left mesiotemporal ROI (amygdala and parahippocampal gyrus: $x = -20$, $y = -10$, $z = -20$, $k = 49$, $p = .04$). Compared to the patients with rTLE, the healthy subjects had significantly more activation within the right ROI (amygdala and anterior hippocampus: $x = -20$, $y = -14$, $z = -18$, $k = 397$, $z = 4.64$, $p<.001$) and also stronger activation within the left ROI (anterior hippocampus: $x = -26$, $y = -12$, $z = -22$, $k = 57$, $z = 4.64$, $p<.001$).

Neither the patients with lTLE nor the patients with rTLE had clusters of stronger mesiotemporal activation compared to the healthy subjects.

Comparing patient groups directly, patients with lTLE tended to have stronger activations within the right mesiotemporal region (amygdala and anterior hippocampus: $x = 28$, $y = -2$, $z = -14$, $k = 36$, $z = 3.47$); however, this difference failed to reach significance ($p = .06$). Patients with rTLE did not have clusters of stronger activation within the mesiotemporal ROI compared to the patients with lTLE.

Table 2
Results of the whole-brain analyses in the three groups (one-sample t-test, activation > rest; all results were significant at p < .001, FWE-corrected). Results show a widespread bilateral network of temporal, occipital, and frontal brain activations in healthy subjects. Patients with lTLE predominantly activated the right-sided temporal parts of this network, whereas patients with rTLE primarily activated posterior brain regions.

Region	Hemisphere	Cluster size k	MNI coordinates			z-Score
			x	y	z	
Healthy subjects						
Inferior and middle occipital gyri, inferior temporal gyrus	r	1007	44	−64	8	6.73
Inferior occipital gyrus, middle temporal gyrus	l	564	−64	−72	10	6.42
Inferior occipital gyrus, inferior temporal gyrus, fusiform gyrus	r	281	40	−44	−20	6.13
Anterior hippocampus, amygdala	r	57	34	−12	−18	5.87
Anterior hippocampus, amygdala	l	104	−18	−12	−18	5.7
Hippocampus, parahippocampal gyrus	r	21	18	−14	−20	5.33
Superior and middle temporal gyri	r	68	54	−40	14	5.36
Fusiform gyrus	l	26	−44	−56	−20	5.24
Precentral gyrus, middle frontal gyrus	r	71	46	6	40	5.59
Inferior frontal gyrus (triangular gyrus)	r	42	48	22	20	5.26
Patients with lTLE						
Middle and superior temporal gyrus, supramarginal gyrus	l	239	−62	−48	20	6.31
Inferior and middle temporal gyrus	r	286	42	−86	−12	5.79
Middle temporal gyrus, supramarginal gyrus	r	186	54	−38	18	5.78
Inferior temporal gyrus	r	124	46	−50	−28	5.46
Superior frontal gyrus	l	43	−10	56	26	6.15
Patients with rTLE						
Inferior and middle occipital gyrus, inferior temporal gyrus, lingual gyrus	r	591	44	−76	−8	6.81
Inferior and middle occipital gyrus, middle temporal gyrus, fusiform gyrus	l	237	−42	−68	−26	5.75

l = left hemisphere, r = right hemisphere.

3.3. Correlations of fMRI activation with behavioral data

We calculated regression analyses using the individual behavioral data (fear intensity and arousal ratings) as covariates in order to test whether they correlated with brain activity from the contrast activation > rest in each group. Regression analyses were calculated within the whole brain and within the mesiotemporal ROI (thresholded at p < .001, uncorrected).

In the patients with lTLE, we did not find significant correlations between fear intensity and arousal ratings and brain activation, neither in the whole brain nor in the ROI analysis.

In the patients with rTLE, we found a positive correlation between the fear intensity rating and fMRI activity in the right inferior lateral parietal lobe (supramarginal and angular gyri: x = 54, y = −60, z = 34, k = 132, z = 4.11, p = .002) and in the orbitofrontal cortex bilaterally (medial frontal gyrus: x = 2, y = 32, z = −16, k = 82, z = 4.08, p = .009). In patients with rTLE, we found a negative correlation between activation and fear intensity ratings in the right frontotemporal junction/anterior insula (inferior frontal and superior temporal gyri, x = 44, y = 12, z = −12, k = 70, z = 4.06, p = .015), i.e., lower fear ratings were correlated with more activation in this region. The arousal ratings of the patients with rTLE were positively correlated with activations on the left superior and middle temporal gyri (x = −68, y = −34, z = 2, k = 101, z = 4.45, p = .004) and on the right superior temporal gyrus and insula (x = 40, y = −32, z = 0, k = 57, z = 4.04, p = .025). We did not find significant correlations of ROI activations and arousal ratings in patients with rTLE.

In healthy subjects, stronger activations on the right inferior lateral parietal lobe (x = 56, y = −38, z = 40, k = 255, z = 4.46, p < .001), the left middle and superior temporal gyri (x = −68, y = −32, z = 2, k = 154, z = 4.29, p = .001), and on the right superior frontal gyrus (x = 20, y = 54, z = 24, k = 75, z = 3.89, p = .018) were correlated with higher fear intensity ratings. No positive or negative correlations with the arousal ratings were observed in healthy subjects.

3.4. Lateralization data

To further test our hypothesis of asymmetrical mesiotemporal activations in patients with TLE, we calculated individual LIs within the mesiotemporal and the amygdala ROI. We did not find activations within the mesiotemporal ROI in 1 patient with lTLE and in the amygdala ROI in 2 patients (1 patient with lTLE, 1 patient with rTLE) when using the adaptive LI calculation procedure. All control subjects exhibited activations in the two ROIs (all subjects had activated voxels on the left and the right side of both ROIs). To analyze between-group differences of relative mesiotemporal activation strength, we calculated

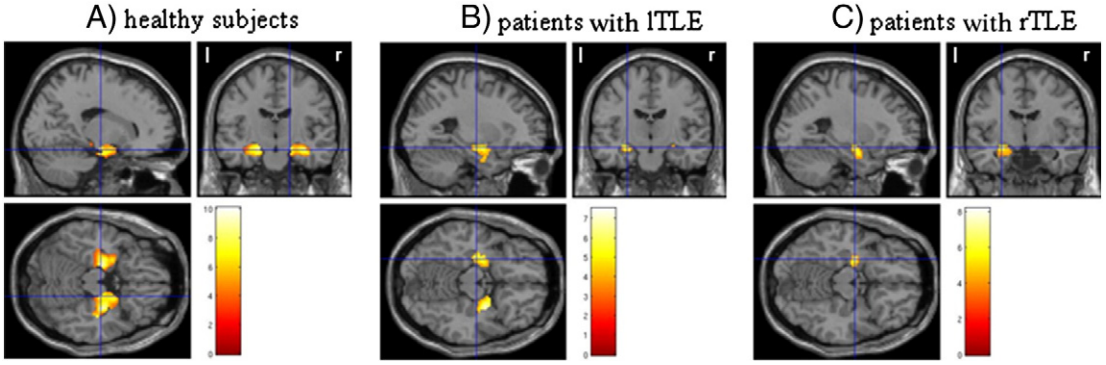

Fig. 2. fMRI activations in the mesiotemporal ROI (one-sample t-tests, activation > rest) in the healthy subjects (A), the patients with lTLE (B), and the patients with rTLE (C).

a univariate ANOVA for the mesiotemporal LIs and for the amygdala LIs. There was a significant main effect for the LIs of the larger mesiotemporal ROI including activation within the amygdala, the hippocampus, and the parahippocampal gyrus ($F = 3.38$, $df = 2$, $p = .04$). The LIs of patients with lTLE showed a right-sided lateralization (mean LI = −.13, SD = .28) and differed significantly from the left-lateralized patients with rTLE (mean LI = .12, SD = .38; $p = .05$). The healthy subjects' LIs (mean LI = −.06, SD = .20) were not significantly different from those of the patients with rTLE ($p = .18$) and lTLE ($p = .80$).

We also found a significant between-group effect for the amygdala ROI ($F = 5.58$, $df = 2$, $p = .006$). The LIs of the patients with lTLE showed a right-sided lateralization (mean LI = −.17, SD = .48) and differed significantly from the LIs of the patients with rTLE with left-lateralized LIs (mean LI = .28, SD = .53; $p = .01$). The LIs of the patients with lTLE did not differ significantly from the healthy subjects' LIs (mean LI = .12, SD = .30; $p = .69$). The LI of the patients with rTLE was significantly more left-lateralized than that of the healthy subjects ($p = .01$).

The large standard deviation within each group indicated that there was a high within-group variance of the individual LIs, i.e., not all of the patients with lTLE had right-lateralized activations within the ROIs. Similarly, not all patients with rTLE showed a dominance of left-sided fMRI activations (see Additional analysis).

3.4.1. Correlations with the LIs

We did not find significant correlations between the LIs and arousal and fear ratings within the three groups. However, in patients with lTLE, we found a negative correlation of $r = -.48$ of medium to large effect size between the amygdala LIs and fear ratings. A lateralization towards the nonepileptic right amygdala was associated with higher fear ratings (see Table 3). The LIs were not correlated with age at seizure onset or epilepsy duration, neither in the patients with rTLE nor in the patients with lTLE (all $r < .25$, all $p > .35$).

3.5. Additional analysis

To further test for an association between amygdala activation lateralization and fear ratings, we used the individual amygdala LIs to classify the patients as being 'typically' or 'atypically' lateralized. According to the groups' fMRI results and the mean amygdala LIs within the groups, relatively stronger activations in the amygdala ROI contralateral to the side of seizure onset were classified as typical (i.e., patients with rTLE showing left-sided lateralization, LIs: >0 to +1 and patients with lTLE showing right-sided lateralization, LIs: <0 to −1). In the event of relatively stronger activations within the epileptogenic temporal lobe, a patient was classified as atypical. In the patient group with lTLE, 6 patients were atypically lateralized in the amygdala ROI (11 with typical lateralization). In the patient group with rTLE, 6 patients had atypical amygdala lateralization (12 with typical lateralization). Then, we compared the fear ratings of patients with typical and atypical lateralization independent of side of seizure onset. We did not find a difference of fear ratings between patients with typical (mean = 4.40, SD = 1.0) and atypical (mean = 3.99, SD = 3.99, $p = .34$) lateralization. We also conducted this comparison within the group with lTLE and group with rTLE, separately. As this is a rather exploratory analysis due to the small number of patients in each group, we calculated effect sizes (Cohen's d) for each comparison. In the group with lTLE, there was a tendency of higher fear ratings in those patients with a typical lateralization (mean = 4.95, SD = 0.84) compared to those patients with atypical amygdala LIs (mean = 4.02, SD = 1.65, $p = .21$). The effect size calculation indicated a large effect ($d = .89$). In the group with lTLE, typical patients' fear ratings did not differ from those of the healthy subjects (mean = 5.02, SD = 0.86, $p = .88$, $d = 0.08$) but atypical patients' ratings did ($p = .09$, large effect size $d = .76$). In the patients with rTLE, we did not find a difference in fear intensity rating between typical (mean = 3.95, SD = 0.88) and atypical (mean = 3.97, SD = 0.95, $p = .96$, $d = .02$) patients. The fear ratings of both subgroups with rTLE were significantly lower compared to the ratings of the healthy subjects ($p \leq .02$, $d \geq 1.15$).

Table 3
Correlations (r) of the LIs with the post-fMRI ratings (all $p > .05$).

	Patients with lTLE		Patients with rTLE		Healthy subjects	
	Fear	Arousal	Fear	Arousal	Fear	Arousal
Amygdala LI	−.48	.24	−.19	.06	.23	−.04
Mesiotemporal LI	−.26	−.04	.31	.31	−.19	−.37

4. Discussion

When viewing dynamic fearful faces, healthy control subjects activated a temporal and extratemporal network known to be involved in emotion processing [18–20]. The patient groups activated different parts of this network. Beyond relatively stronger right-sided mesiotemporal activations, patients with lTLE activated right-hemispheric temporolateral brain regions and had fear ratings comparable to those of healthy subjects. Patients with rTLE had lower overall brain activations compared to healthy subjects and patients with left-sided TLE. The activations observed in patients with rTLE occurred predominantly in emotion-unspecific posterior brain regions, bilaterally. Behaviorally, the patients with rTLE showed the weakest fear ratings. Concerning the mesiotemporal fMRI activations, we mainly replicated the earlier findings of Schacher et al. [12]. On the group level, we found relatively stronger right-sided mesiotemporal activations in patients with lTLE, stronger left-sided mesiotemporal activations in patients with rTLE, and bilateral and symmetrical activations in healthy subjects associated with viewing fearful faces. In accordance with the results of Benuzzi et al. [14] and Batut et al. [15], we found the weakest activations in the group of patients with rTLE. However, this result is divergent from the findings by Bonelli et al. [16], who did not find mesiotemporal activations in patients with lTLE in an affective face paradigm.

We correlated mesiotemporal LIs with the subjective evaluation of the stimuli presented. In patients with lTLE, we found a negative correlation of medium effect size ($r = -.48$) between the amygdala LIs and fear ratings in the group with lTLE. Relatively stronger right-sided amygdala activations were associated with higher fear ratings, comparable to those of healthy subjects. Stronger fMRI involvement of the right amygdala in the event of left mesial temporal lobe damage was thus associated with normal fear intensity ratings. In atypical patients with lTLE (i.e., with relatively stronger left-sided amygdala activity), fear ratings were lower compared to those of healthy subjects. Thus, in patients with lTLE, activations of the left mesial temporal structures together with right-sided temporolateral areas are sufficient to preserve normal facial fear ratings in the event of left-sided mesiotemporal damage. Although 12 of 18 patients with rTLE also had stronger activations in the amygdala contralateral to the side of seizure onset, this pattern does not reflect successful compensation. There was no correlation between mesiotemporal/amygdala lateralization and fear intensity ratings. Both subgroups with rTLE, patients with typical and atypical amygdala activation lateralization, had significantly lower fear ratings than healthy subjects. Thus, relatively stronger involvement of the left amygdala cannot compensate for the function the right amygdala has. Impaired fear evaluation in patients with right-sided limbic damage is in accordance with the traditional hypothesis that right mesiotemporal structures are involved more crucially in decoding and recognizing negative emotions compared to left mesiotemporal regions (e.g., [21–23], but see also [24]). The vulnerability for deficits in negative facial emotion processing caused by right-sided mesiotemporal lesions is also supported by most of the studies assessing affect recognition in patients with TLE. Meletti et al. [7] showed that 53%

of the patients with rTLE had emotion recognition performances 2 SDs below the performance of healthy subjects. These reductions were observed in only 17% of the patients with lTLE. More pronounced emotion-recognition impairment in patients with TLE with a right-sided compared to left-sided mesial lesion was also reported by other studies [8,25,26]. Furthermore, in patients with partial epilepsies and comorbid anxiety disorder, right-sided, but not left-sided, mesiotemporal regions seem to show abnormally increased volumes [27].

Although we found the relative mesiotemporal activity (LI) to be correlated with fear ratings in patients with lTLE, we did not find correlations between the absolute right or left amygdala activation and the rating data, neither in the patient groups nor in healthy subjects. This is in accordance with the recent study of Straube et al. [28] who used a similar fMRI paradigm with threatening scenes from horror movies in healthy subjects. They did not find a correlation between absolute amygdala activations and anxiety ratings. Comparable to our result in healthy subjects, they found a positive correlation between subjective anxiety ratings and activation within the dorsomedial prefrontal cortex (very similar to the region we found to be correlated with fear intensity ratings in our healthy subjects). Activation in the dorsomedial prefrontal cortex has been shown to be involved in directing attention to emotional stimuli, evaluation and (re)appraisal of emotional stimuli and situations, and fear conditioning [29,30]. Straube and colleagues [28] concluded that the dorsomedial cortex is crucial for the experience of scare. This is in accordance with the results of Holtz et al. [31] showing dorsomedial activations to be associated with the anticipation of physical threat (hyperventilation). In their study, dorsomedial activation was more pronounced in subjects who experienced demanded hyperventilation more aversive and fearful, than in those who experienced less discomfort during hyperventilation. Somatic fear symptoms were positively correlated with activation in the dorsomedial prefrontal cortex and the anterior insula. They also found left-sided activations of the middle and superior temporal gyri to be linked to fear-conditioning, a region we found to be positively correlated with anxiety ratings in healthy subjects and in the group with rTLE in our study.

In patients with rTLE, we also found a correlation of fear ratings with bilateral activation in the medial prefrontal cortex, but compared to the healthy subjects, the region was located more inferiorly in the ventromedial area of the prefrontal cortex. In their elaborate review on the involvement of different medial frontal brain regions in aspects of affect processing, Etkin et al. [30] reasoned that the ventromedial part of the prefrontal cortex is activated in fear extinction and in the top-down regulation of emotional conflicts. The ventromedial prefrontal cortex seems to inhibit negative affect processing, i.e., by suppressing limbic activity. This is also supported by neuroimaging studies in patients with anxiety disorders. In symptom provocation studies, higher amygdala activation cooccurred with reduced ventromedial prefrontal cortex activity [32–34]. Psychotherapy leading to anxiety reduction might upregulate the mediofrontal hypoactivity and concurrently downregulate amygdala hyperactivation [35–37]. Based on the assumed fear-inhibiting role of the ventromedial prefrontal cortex, higher ventromedial prefrontal cortex activations associated with lower fear ratings could be expected. However, in the group with rTLE, we found stronger activations to be associated with higher fear ratings. This could be the consequence of a reduced responsiveness of the damaged right mesiotemporal structures to frontal activations. Together with the different pattern of involved brain regions in patients with rTLE (compared to healthy subjects), the results imply broader functional disturbances within emotion-specific brain regions also remote to the structurally damaged right mesiotemporal region.

It is conceivable that frontolimbic dysregulations might be the common basis for both emotion-recognition impairment and psychiatric conditions in patients with TLE. Compared to the healthy population, patients with TLE have an increased prevalence of psychiatric disorders, specifically major depression and anxiety disorders [38,39]. Most likely, psychiatric comorbidities are more frequent in patients with TLE compared to extratemporal epilepsies, also underlining the crucial role of the limbic structures in feelings of anxiety and in mood disorders [40]. Some, but not all, studies found that patients with rTLE had a higher risk for the development of mood and anxiety disorders compared to patients with lTLE ([41,42], but see also [43]). Disturbances in affect processing are a common feature in patients with psychiatric disorders. Several experimental studies in psychiatric patients with depression or anxiety disorders have shown impairment in recognizing affective facial expressions, including fear (e.g., [44,45]). As mentioned above, in patients with anxiety disorders and depression, affective alterations in response to negative stimuli were discussed to be a result of hyperactivity of the amygdala in concert with reduced prefrontal activity [30,33,46,47]. A similar corticolimbic dysregulation is proposed in patients with depression [48–50]. Beyond functional alterations, structural changes within limbic structures were also reported in these psychiatric conditions [51–54]. Bonelli et al. [16] reported a link between presurgical fMRI activity induced by viewing fearful faces and presurgical levels of anxiety and depression in right-sided but not in left-sided patients with TLE, supporting the assumption of a potential association between the neural correlates of affect processing and levels of depression and anxiety. Emotion recognition and processing deficits (and subsequent interactional and behavioral problems) might thus represent a vulnerability factor, i.e., these deficits might turn into a psychiatric condition when there is an additional lack of internal coping mechanisms and/or social support.

We also found superior temporal/posterior insula activations to be positively correlated with fear ratings in healthy subjects and with arousal ratings in patients with rTLE. Superior temporal and insula activations have been reported in a number of symptom provocation fMRI paradigms in patients with anxiety disorders [55,56] and anxiety provocation or fear learning in healthy subjects [57,58]. The posterior part of the insula is involved in the integration of sensory information and arousal states. It collects emotional, interoceptive, and environmental data which are integrated in the anterior part of the insula (see [59–61] and metanalysis by Cauda et al. [62]). The insula is suggested to subserve the interface between mapping external stimuli, physical arousal, and forming this into a subjective feeling. In patients with rTLE, we found a correlation of fear intensity ratings with right-sided activations in the right anterior part of the insula. Surprisingly, this correlation was negative, i.e., lower fear ratings were associated with stronger insula activation. This contradicts fMRI studies reporting insula activations (not deactivations) in fMRI tasks using fearful stimuli that were found to be more pronounced in subjects with higher fear scores compared to lower fearful subjects [63,64]. Thus, although we found a tendency towards higher arousal ratings in patients with rTLE with relatively stronger left-sided mesiotemporal activations and a positive correlation between absolute posterior temporolateral activations and arousal intensity ratings, this was not associated with normal fear intensity ratings. The negative correlation between right anterior insula activation and fear ratings might further indicate that the processing of affective arousal and the subsequent development and/or perception of a fear experience are disturbed. This is rather speculative as we did not assess physiological arousal parameters, such as skin conductance response. However, studies with patients with unilateral amygdala damage suggest that the arousal component of emotion processing is actually impaired [65,66].

Taken together, our results in the patients with rTLE indicate that reduced fear ratings are caused by a functional dysregulation of the brain network underlying emotion recognition, arousal integration, and affect regulation. This disturbance functionally involves more than the affective mesiotemporal core structures of the lesioned temporal lobe but comprises frontomedial and temporolateral brain regions. The assumption of a disturbed interaction of limbic and cortical areas involved in emotion processing deficits is supported by studies measuring functional connectivity in patients with rTLE. Recently, Pittau

et al. [67] reported a decreased connectivity between the right amygdala and hippocampus and, amongst others, the right ventromedial prefrontal cortex (exactly corresponding to the region we found to be correlated with fear ratings in patients with rTLE) in patients with rTLE in their resting-state study. Broicher and colleagues determined functional connectivity in patients with TLE who were watching the fearful faces of the paradigm used in the current study [68]. Beyond reduced connectivity within the amygdala–hippocampus complex, the authors found reduced coactivation between the amygdalae and the lateral temporal lobe and two left-sided mesiofrontal brain regions in patients with rTLE compared to healthy subjects.

4.1. Limitations

As we used a task including fearful faces only, we could not generalize our findings to other emotions. Further, the assessment of the subjective stimuli evaluation was conducted after the scanning procedure. We did so in order not to interrupt ongoing affect processing during the scanning procedure by a direct rating following each stimulus. However, the ratings might be falsified because of the post hoc rating procedure we chose. Our fMRI results are based on a rather wide contrast comparing activations induced by watching fearful faces and activations induced by landscapes. This wide contrast was chosen because we were interested in inducing preferably strong activation in the mesiotemporal regions (e.g., to test our lateralization hypotheses, a common approach in epilepsy fMRI research). In future studies, a third condition including emotionally neutral dynamic faces could be added. In addition to the evaluation of the arousal dimension, it would be interesting to assess physiological parameters, such as skin conductance responses during the scanning procedure in future studies.

Although our results suggest that left-sided mesiotemporal damage is accompanied by relatively stronger involvement of the right-sided mesiotemporal and temporolateral brain region, this pattern was not observed in each patient. On the individual level, we did not replicate a reliable asymmetrical lateralization contralateral to seizure onset as shown by Schacher et al. [12] and, although less reliable, by Broicher et al. [13]. Schacher and colleagues reported this asymmetrical mesiotemporal pattern in 11 of 12 patients. In our study, 12 patients of those 35 patients with individual amygdala activations were classified as 'atypical', i.e., having relatively stronger activations in the ipsilateral amygdala. Occurrence of atypical lateralization was independent of side of seizure onset as it was found in about 35% of the patients of both patient groups.

4.2. Conclusion

In healthy subjects, the whole-brain fMRI results showed a typical network of mesiotemporal, temporolateral, and frontal brain regions known to be involved in fear processing. Patients with lTLE had normal fear ratings and activations in the mesiotemporal and temporolateral parts of this network, mainly within the right hemisphere. In those patients, we found a negative correlation between relative amygdala activations and fear ratings, indicating that a relatively stronger involvement of the right amygdala (proposed to be biologically predisposed to processing negative affect) is sufficient to preserve normal fear evaluation. This kind of successful compensation was not found in patients with rTLE. They had the weakest fMRI activations, which occurred predominantly in posterior brain regions not specifically involved in fear processing. They also had reduced fear ratings compared to healthy subjects. Thus, we conclude that more severe deficits in emotion processing observed in several behavioral studies in the event of right-sided compared to left-sided mesiotemporal damage are caused not only by the right limbic damage but also by additional functional disturbances of the cortical network underlying affect processing. This underlines the apparent specific necessity of intact right-sided mesiotemporal areas for unimpaired fear processing.

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