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Association between structural abnormalities and fMRI response in the amygdala in patients with temporal lobe epilepsy

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ABSTRACT

Objective: The goal of this study was to investigate whether dysplastic amygdalae show an impaired response as revealed by functional MRI (fMRI).
Methods: A fearful face fMRI paradigm using video sequences, as we have recently applied, was used in 25 patients with temporal lobe epilepsy (TLE): 24 had mesial TLE (14 right-, nine left-sided, one bilateral); one left lateral neocortical TLE. T1-, T2-weighted and fluid attenuated inversion recovery (FLAIR) MRI sequences were assessed for the detection and categorisation of structural amygdalar abnormalities according to size and MR signal intensity. Of the 25 patients, five patients had probable dysplastic amygdala (pDA): two right- and three left-sided.
Results: A fearful face paradigm led to significant amygdalar activation in all but one patient ($p < 0.05$). In 15 (60%) of the patients amygdalar activation was found contralateral and in four (16%) ipsilateral to the side of seizure onset. Bilateral amygdalar activation was registered in five (20%) patients. In two patients with right-sided and one with left-sided pDA, fMRI activation was observed only in the contralateral amygdala. In two out of three patients with left-sided pDA we found significant ipislateral amygdalar fMRI-responses.
Conclusion: Unilateral pDA does not necessarily affect the amygdalar fMRI BOLD-response.

1. Introduction

The amygdala-complex is considered to be a pivotal component of processing of stimuli with emotional and social significance.[1,2] It modulates neuronal systems in response to perception of such stimuli which govern cognitive and social behavior.[3] Dysfunction of the human amygdala has been implicated in disturbances of memory, attention, impaired ability to evaluate emotional situations, autism, depression, narcolepsy, posttraumatic stress disorders and phobias.[4] Amygdalar lesions are associated with epilepsy, Alzheimer's disease,[5] schizophrenia[6] and Urbach-Wiethe syndrome, a rare genetic disorder with calcified amygdalae.[7]

In patients with mesial temporal lobe epilepsy (mTLE), amygdalae are often part of the epileptogenic zone and, in about a quarter of patients with hippocampal sclerosis (HS), the ipsilateral amygdala shows volume reduction or even atrophy.[4,8] In addition, an association has been observed between epilepsy duration and the extent of amygdala volume loss.[9]

A dysplastic amygdala may appear as abnormal in structural MRI, with increased volume and high MR signal in T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences.[10] Similar MRI features are common in limbic encephalitis affecting mesio-temporal regions.[11,12] However, in the majority of patients with limbic encephalitis, they present with initial swelling of the mesio-temporal area with subsequent evolution from signal increase and enlargement to atrophy over several months.[12,13]

Another cause of mesio-temporal volume increase and high MR signal in T2 and FLAIR could be a high grade glial tumor characterized by contrast enhancement and progression over time. Low grade glial tumors are the most challenging to differentiate from dysplasia, since they are not frequently enhanced by contrast and remain stable over a long period of time.

Functional organization of cortical dysplasias and other malformations of cortical development (MCD) have been assessed non-invasively by functional MRI (fMRI) and different patterns of fMRI activity have been observed: MCD caused by disturbances of cortical organization showed activity during simple motor tasks, whereas in MCD due to disturbances of earlier steps of cortical development, e.g. cortical dysplasia Palmini type II,[14] activity was shifted to unaffected cortical areas in over 50% of patients.[15]

fMRI studies have demonstrated a major role of the amygdala in the processing of emotions by responsivity to fearful facial expressions.[16,17] In contrast to static photographs,[16] an animated fearful face paradigm[17] activated the amygdalae bilaterally in all

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Table 1
Demographic, epilepsy, MRI and fMRI data of 25 patients with temporal lobe epilepsy.

Patients	Sex	Age	Age at seizure onset [y]	Duration of epilepsy [y]	Seizure frequency[a]	Side of seizure onset	Morphologic lesion	Amygdala activation	LI	*p*-Value	Language	Handedness (right/left)
1	m	46	29	17	M	Right	HS	Unilat. left	1	0.05	Left	RH
2	w	46	14	32	M	Right	HS	Unilat. left	1	0.001	Left	RH
3	m	33	8	25	D	Right	HS	Unilat. left	1	0.001	Left	RH
4	m	56	42	14	W	Right	HS	Unilat. left	1	0.01	Left	RH
5	m	53	2	51	M	Right	HS	Right > left	−0.51	0.001	Bilateral	Ambidexter
6	m	43	37	6	W	Right	HS	Unilat. left	1	0.01	Left	RH
7	w	57	27	30	M	Right	HS	Bilateral	−0.10	0.01	Bilateral	RH
8	w	25	21	4	W	Right	HS; pDA	Unilat. left	1	0.001	Left	RH
9	w	48	7	41	M	Right	HS; AA	Right > left	−0.74	0.05	Left	RH
10	m	26	26	3	W	Right	pDA	Unilat. left	1	0.001	Left	RH
11	w	44	3	41	W	Right	HS; FCD frontobasal	Unilat. left	1	0.001	Left	RH
12	m	47	10	37	M	Right	HS; arachnoid cyst temporo-polar left	Left > right	0.49	0.001	Left	RH
13	w	60	45	15	M	Right	Small cystic lesion adjacent to right amygdala	Bilateral	−0.13	0.05	Left	RH
14	w	29	6	23	M	Right	HS; cavernoma temporal	Bilateral	0.11	0.01	Left	RH
15	w	42	19	23	D	Left	HS	Unilat. left	1	0.001	Left	RH
16	w	30	11	19	D	Left	HS	Unilat. right	−1	0.001	Left	RH
17	m	35	2	33	D	Left	HS	Right > left	−0.82	0.001	Left	RH
18	m	16	4	12	D	Left	HS	Bilateral	−0.24	0.001	NA	RH
19	w	49	5	44	M	Left	HS	Unilat. right	−1	0.001	Left	RH
20	w	45	9	36	D	Left	HS	Unilat. right	−1	0.001	Left	RH
21	m	32	5	27	W	Left	HS; pDA	Right > left	−0.67	0.01	Left	RH
22	m	41	23	18	M	Left	HS; pDA	Bilateral	−0.01	0.01	Left	RH
23	m	17	4	13	W	Left	HS; ulegyria occipital	Unilat. right	−1	0.001	Left	RH
24	m	21	11	10	W	Bilateral	HS; AA	NA	0	NA	Left	RH
25	w	16	12	4	M	Left	HS; pDA; cavernoma temporolateral	Left > right	0.82	0.001	Left	RH

m – man, w – woman, y – years, M – monthly, D – daily, W – weekly, HS – hippocampal sclerosis, pDA – probable dysplastic amygdala, AA – amygdala atrophy, FCD – focal cortical dysplasia, unilat. – unilateral, LI – lateralization index, NA – not applicable.
[a] Seizure frequency at the time of fMRI test.

the 17 healthy controls, whereas the majority of patients (11 out of 12) with unilateral temporal lobe epilepsy (TLE) and HS showed amygdalar activation contralateral to the seizure onset side. However, in some patients, dissociations between amygdalar activations and epileptogenic lesion were found.[17] Schacher et al.[17] reported that in two patients ipsilateral amygdala activity and reversed asymmetries in parahippocampal activations were observed.

Here, we investigate for the first time, whether amygdalar response in fMRI is principally impaired if it is affected by dysplasia-like structural abnormalities as defined by stationary but increased volume in T1-, and signal enhancement in T2-weighted and FLAIR MRI sequences.

2. Methods

2.1. Participants

Twenty-five patients aged 16–60 (mean 38 years, SD 13.2; 13 men, 12 women; 24 right handed and 1 ambidexter) with TLE (mean age at seizure onset 15.2 years, SD 12.7 and epilepsy duration 23.1 years, SD 13.7) were investigated (see Table 1). Patients were recruited from consecutive inpatient admissions to the Swiss Epilepsy Center.

All the patients underwent neurological examination and routine EEG recordings using the 10-20 system.[18] Seizure types and epilepsy syndromes were diagnosed according to the classification of the International League Against Epilepsy.[19,20] Seizure onset zone was determined by continuous interictal and ictal video/EEG monitoring with scalp and sphenoidal electrodes.

All the patients had mTLE. Nineteen patients had HS (18 unilateral and one bilateral). All the patients had pharmacoresistant epilepsy (14/25 patients had daily or weekly seizures) (see Table 1).

Language laterality was determined either by use of an fMRI paradigm employing a verbal fluency task[17] ($n = 23$) or by Wada test if the fMRI was inconclusive ($n = 2$).[21] The majority of patients (23/25) had left-sided language dominance, two had bilateral language representation. Handedness was determined by the Edinburgh Handedness Inventory.

Every patient gave written informed consent after a complete explanation of the study. The present study was performed in adherence to the Declaration of Helsinki and was also approved by a local medical ethics committee.

2.2. fMRI task design

The fMRI paradigm used here was first developed, validated and applied to healthy controls and patients with TLE by Schacher et al.[17] Further information related to the selection procedure of the stimuli can be found in Schacher et al.[17] The block design paradigm consisted of eight activation and eight baseline blocks each lasting 24 s. The activation condition comprised 75 brief episodes (2–3 s) from thriller and horror films. All the episodes showed the faces of actors who were expressing fear with high intensity. None of the episodes showed violence or aggression. During baseline blocks 72 short episodes of similar length (2–3 s) with dynamic landscape video recordings were presented. Video clips of dull domestic landscapes were used owing to their stable low emotional content while their general visual stimulus properties were comparable with the movie clips. Frequency and duration of the sequences (2–3 s) were matched in the activation and control conditions. Stimuli were presented via a back-projection screen and viewed through a tilted overhead mirror. Prior to beginning, subjects were told that they would see rapid presentations of film sequences depicting fearful faces intermixed with landscape film sequences. They were instructed to

relax while watching the film and to focus on the eyes of the actors during the activation blocks.

2.3. MRI acquisition

The fMRI data were recorded using a 3.0 T Achieva scanner (Philips Medical Systems, Best, The Netherlands) between 2007 and 2009 using a standardized protocol. MRI sequences included T1-weighted spin echo and gradient echo three-dimensional multiplanar reconstruction images (MPRAGE) with and without intravenous contrast application, coronal T2-weighted turbo spin echo, T2-weighted fast fluid attenuated inversion recovery (FLAIR) and diffusion weighted sequences. Coronal T2 and FLAIR slices were 1–3 mm thick and were acquired at 90° perpendicular to the long axis of the hippocampus. Subjects were sited in the head coil with ear pads and foam padding to minimize head motion. There were successive parameters for the anatomic sequence: 176 axial slices with 1-mm single-slice thickness, repetition time (TR) 8.2 s, echo time (TE) 3.93 s, 8° flip angle, field of view (FOV) 250 mm, and 288 × 288 matrix.

Functional data were acquired using EPI T2*-weighted sequence. The following parameters were applied to measure amygdalar activation: 18 coronal slices, 4-mm slice thickness (interslice gap: 0 mm), TR 1500 s, TE 35 s, 75° flip angle, FOV 220 mm, matrix size 64 × 64 (voxel size 2.75 mm × 2.75 mm × 4 mm), reconstructed into an image matrix of 128 × 128. Coronal slices were geared orthogonally to the hippocampal formation and were spread over the anterior temporal lobe.

2.4. Data analyses

fMRI single subject data analysis was performed with BrainVoyager QX (BrainInnovation, Maastricht, the Netherlands). In the primary analyses the data were preprocessed with (1) three-dimensional motion correction and (2) trend removal by temporal fast Fourier transform-based high-pass filtering and transformed into Talairach co-ordinate area. Images of the fearful face task were additionally spatially smoothed with a full width at half-maximum of 4 mm.

For multiple regression analysis a general linear model (GLM) with the predictor for the activation condition was computed. The time courses of the predictor were obtained by using a linear model of the hemodynamic response. The overall model fit was assessed using *F* statistics. Significant differences between the experimental conditions were assessed using contrast (*t*) maps.

For images in the fearful face task, individual volumes of interests (VOIs) were defined for the amygdalar region.[22,23] VOIs were specified functionally for each patient separately using a predefined statistical threshold of $p < 0.05$; $p < 0.01$ and $p < 0.001$ (see Table 1). Anatomic borders of the functional clusters were the uncal recess of the temporal horn caudally, the optical chiasm rostrally, and white matter superiorly. For each VOI the number of activated voxels was counted in the left and right hemisphere at the lowest reasonable statistical threshold. Lateralization indexes (LI) were defined for the number of meaningful activated voxels in the amygdalar/periamygdalar area using the formula: LI = (left − right)/(left + right). LI between ±0.5 and ±1 was defined to represent strong lateralization and LI between ±0.25 and ±0.5 − weak lateralization (with "−" lateralizing to the right and "+" to the left, respectively). LI between −0.25 and +0.25 was defined as bilateral amygdalar activation.

2.5. Criteria for the assessment of amygdalar structural abnormalities

MRIs were assessed to detect and categorize amygdalar structural abnormalities by two independent raters from different institutions (1. SB with 4 years of experience in fMRI research and evaluation of MRI of patients with epilepsy; Swiss Epilepsy Center, Zurich, Switzerland and 2. GK with 6 years of experience in fMRI research and evaluation of MRI of patients with MCD; Department of Neurology, Innsbruck Medical University, Austria). The raters were blinded with regard to clinical data.

Amygdalae were assessed visually for size (T1-weighthed MPRAGE sequence) and MR signal intensity (T2-weighted and FLAIR sequences). Amygdalae were considered "lesional" if the combination of size and signal abnormalities were observed. Size was assessed in comparison to the contralateral side and was considered abnormal if it was atrophic or pathologically increased. Amygdalar lesions were categorized as:

(1) amygdala atrophy (AA) if it was shrunken (atrophic) with signal increase in T2-weighted and FLAIR sequences;
(2) probable dysplasia (pDA) if the size was pathologically increased with signal increase in T2-weighted and FLAIR sequences; additional MRI features of pDA were white matter volume reduction and increased signal in T2-weighted and FLAIR sequences in ipsilateral temporal lobe; in order to exclude limbic encephalitis the patients should not have had MRI features of swelling at the initial MRI performed at the manifestation of epilepsy and the MRI features had to remain constant over at least two MRIs within an interval of at least 12 months. Only in one patient (patient 10 with right-sided pDA) this interval was less than 12 months. In order to exclude high grade glial tumors there had to be no progression of the disease and no MRI contrast enhancement in T1-weighted post-contrast images. Dysplastic tumors (ganglioglioma, GG and dysembrioplastic neuroepitelial tumor, DNT) were considered under pDA since they are incorporated in the classification of malformations of cortical development[24];
(3) lesions other than AA or pDA.

The following rating scale was proposed, for size: 0 (normal), +1 (slightly enlarged), +2 (moderately enlarged), +3 (considerably enlarged), −1 (small), −2 (moderate atrophy), −3 (severe atrophy); for signal intensity: 0 (normal), 1 (moderately increased), 2 (considerably increased).

Agreement between the two raters (SB, GK) was reached in 23/25 cases (Cohen's kappa coefficient, $\kappa = 0.828$, $p < 0.0001$). Of these 23 patients, 15 could be classified as having normal amygdalae, 5 pDA, 2 AA, and one patient with other amygdalar lesion (a small cystic lesion adjacent to amygdala). In the remaining 2/25 cases, a third evaluator (ET, Department of Neurology, Innsbruck Medical University, Austria) was consulted. The decision was made with two out of three votes; there were no cases with three different rating scores. As a result of the assessment, 17 patients were classified as having normal amygdalae, 5 pDA, 2 AA and one other amygdalar lesion.

2.6. Statistics

Descriptive statistics were used for group comparisons due to the small sample size of the subgroups. Individual fMRI statistics were adopted based on multivariate models as provided by Brain Voyager QX.

3. Results

T2*-weighted contrast differences were found within amygdalae in all the subjects but one in response to watching video sequences with fearful faces in contrast to watching landscape scenes ($p < 0.05$). The activation focus was located in the superior part of the amygdala, as described elsewhere.[17,22,23]

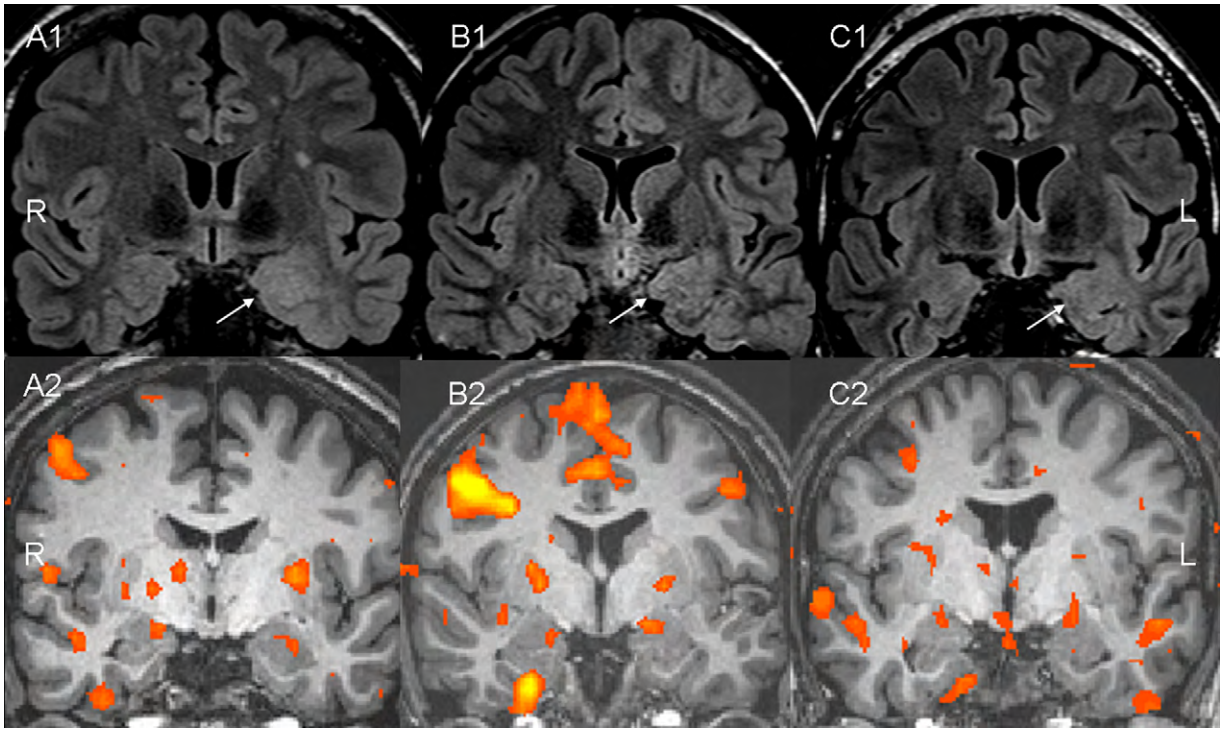

Fig. 1. Patients *N* correspond to the numbers indicated in Table 1. Upper row (A1 – patient N 21, B1 – patient N 25, C1 – patient N 22): coronal FLAIR (fluid attenuated inversion recovery) MRI images of three patients with left-sided amygdala dysplasia (white arrows). Amygdala has increased signal and is enlarged on the left side compared to the right; temporal lobe on the left is smaller and has increased signal in white matter. Lower row – patients with left-sided amygdala dysplasia: A2 (patient N 21) – fMRI BOLD-signal strongly lateralised to the right amygdala (LI −0.67); B2 (patient N 25) – fMRI BOLD-signal strongly lateralized to the left amygdala (LI 0.82); C2 (patient N 22) bilateral fMRI BOLD-signal in amygdala (LI −0.01). R – right; L – left.

Out of the 17 patients with normal amygdala, bilateral amygdalae activation was observed in three (18%) patients (mean LI −0.08), strongly lateralized right-sided activation in six (35%) (mean LI −0.72), strongly lateralized left-sided activation in seven (41%) patients (mean LI 1.00); and in one patient the activation was categorized as weakly lateralized to the left (LI 0.49).

In two patients with right-sided pDA, the activation was observed in the contralateral amygdala (for both LI 1) (Fig. 1); whereas in three patients with left-sided pDA, activations were bilateral ($n = 1$; LI −0.01), ipsilateral with strong lateralization ($n = 1$; LI 0.82) or contralateral with strong lateralization ($n = 1$; LI −0.67) (Fig. 2).

In one patient with right-sided AA, the activation was observed ipsilateral with strong lateralization (LI −0.78), whereas in one patient with bilateral AA no activation was detected. In the patient with the small cystic lesion adjacent to the right amygdala, bilateral amygdala activation was observed (LI −0.13).

Across all the subjects the average LI of amygdalar activation was 0.13 (SD 0.8).

In relation to the seizure onset side, amygdalar activation was contralateral in 15 (60%) patients (14/15 with strong lateralization) and ipsilateral in four (16%) patients (2/4 with strong lateralization). In two patients with left-sided TLE and in three patients with right-sided TLE, amygdalar activation was bilateral. No amygdalar activation was observed in one patient with bilateral mTLE and bilateral HS.

4. Discussion

We present a cohort of 25 consecutive pharmacoresistant TLE patients who were tested by means of an animated fearful faces paradigm that reliably elucidates amygdalar BOLD activation. A previous study has shown that, irrespective of language representation and handedness, this paradigm results in bilateral amygdalar activation in the majority of healthy controls, whereas the activation is mostly contralateral to the side of seizure onset in unilateral symptomatic TLE patients.[17] In our series we were able to reproduce the findings of our previous study[17] using an independent patient sample and a different scanner: the majority of patients (80%) had activation contralateral to the side of seizure onset. However, in four out of 25 symptomatic TLE patients, amygdalar activation was ipsilateral to mesial temporal lesion.

In this study, we aimed to investigate whether mesial temporal lesions observed on MRI could influence the activation pattern in the amygdala. Indeed, in two patients with left-sided pDA, significant activation was detected on the side of the lesion (activation was bilateral in one patient) demonstrating that unilateral pDA does not necessarily cause a loss of amygdalar function as indicated by fMRI BOLD-response. In contrast to these patients, two patients with right-sided and one with left-sided pDA showed strongly contralateral activation. Whether this apparent left right/asymmetry represents functional or structural differences as has been suggested remains speculative due to our small sample size.[25,26]

The histological type of dysplasia could also play an important role in the reactivity of pDA. It is not possible to determine the type of dysplasia based on MRI features since there are no correlative studies available with regard to amygdala imaging and histological features which would validate MRI characteristics of dysplasia affecting amygdalae.

Constant MRI features over a relatively long time period, absence of swelling signs on initial MRI and of contrast enhancement and clinical presentation characteristic for other possible causes of amygdalar lesions (swelling, tumor, or inflammation) enabled us to categorize amygdalar lesion as probable dysplasia.

In patients with pharmacoresistant seizures a precise detection of the extent of an epileptogenic as well as functional deficit zone is

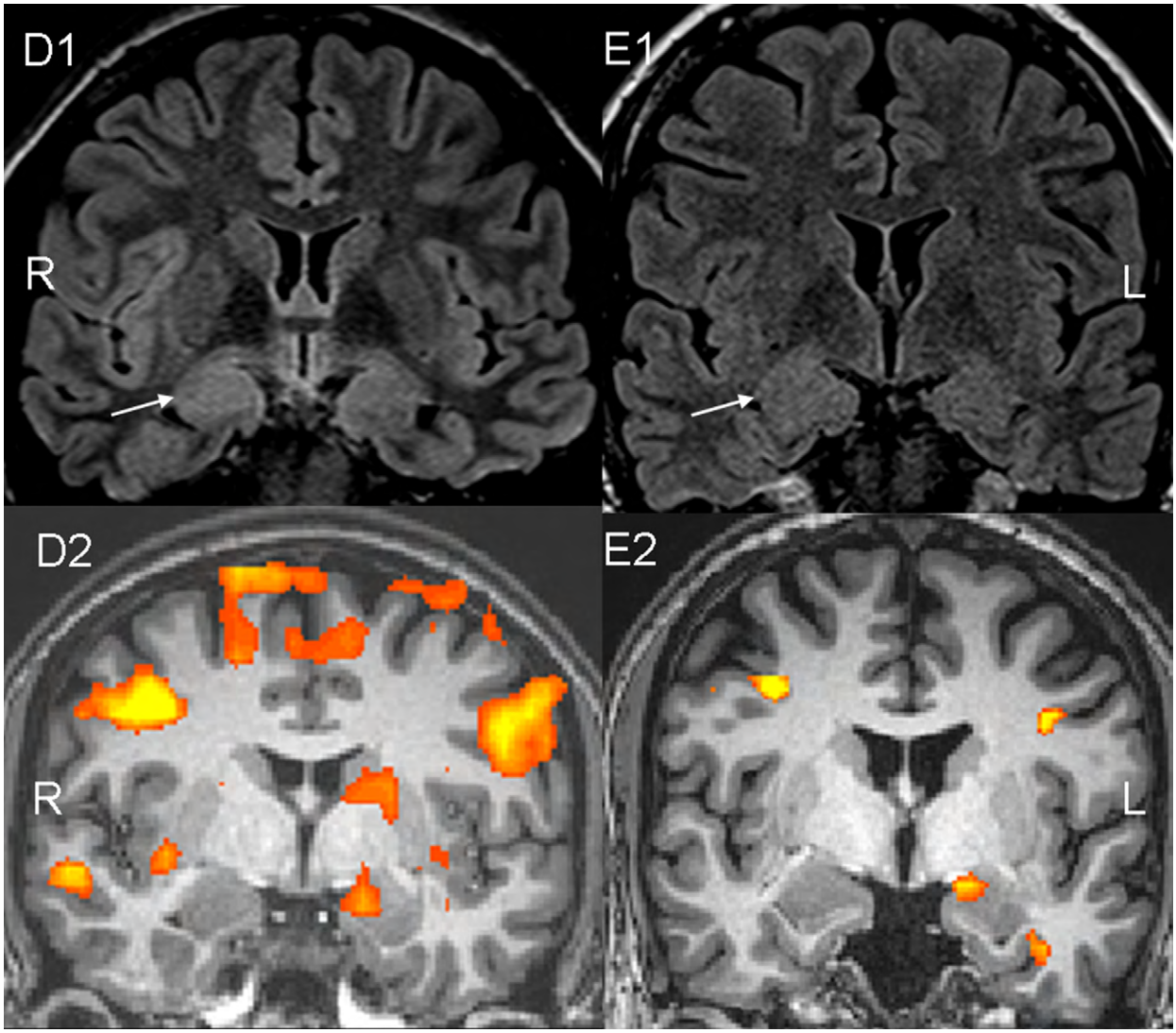

Fig. 2. Patients *N* correspond to the numbers indicated in Table 1. Upper row (D1 – patient N 8, E1 – patient N 10): coronal FLAIR (fluid attenuated inversion recovery) MRI images of two patients with right-sided amygdala dysplasia (white arrows). Amygdala has increased signal and is enlarged on the right side compared to the left. Lower row (D2 – patient N 8, E2 – patient N 10): strongly lateralised left-sided fMRI BOLD-signal, contralateral to dysplasia affecting right amygdala (LI for both cases 1). R – right; L – left.

essential for determining the resection borders in order to achieve seizure freedom without additional postoperative functional deficits.[28] In line with our previous study, we have demonstrated functional response in amygdalae affected by epileptogenic lesions. Bonelli et al.[16] used a fearful face paradigm in mTLE patients for determining whether preoperative amygdalar response could be a potential predictive marker for emotional disturbances following surgery: greater increases in anxiety and depression were observed in patients who had greater preoperative amygdalar activations.[16] It is well established that psychosocial difficulties and psychiatric dysfunctions appear more often in patients with mTLE compared to other chronic epilepsy syndromes.[29,30]

Abnormalities in higher social cognition were found in both pre- and postoperative mTLE patients.[31] Based on the lesion and functional imaging studies, Kirsch[32] has highlighted the specific role of temporal lobe structures in social cognitive processes and indicated possible impairments in higher-order social behavior due to an anterior temporal lobectomy. However, another preliminary prospective study on social cognition did not reveal changes caused by anterior temporal lobectomy.[33]

In summary, the results of this explorative study indicate that in TLE patients unilateral amygdala dysplasia-like structural abnormalities does not necessarily affect the amygdalar fMRI BOLD-response, but does frequently induce a shift of fMRI BOLD-signal to the contralateral side. However, for further delineation of response characteristics in dysplastic amygdala and its functional importance, a larger number of patients and pre- and postsurgical evaluations, including histopathology, are required.

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