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ORIGINAL COMMUNICATION

Alterations in functional connectivity of the amygdala in unilateral mesial temporal lobe epilepsy

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Abstract The aim of this work was to evaluate the relationship between ipsilateral amygdala dysfunction in unilateral mesial temporal lobe epilepsy (MTLE) and remote temporal, frontal, and parietal brain structures and to identify their association with theory of mind (ToM) abilities. Functional magnetic resonance imaging (fMRI) data were acquired from MTLE patients with unilateral hippocampal sclerosis ($n = 28$; 16 left-sided) and healthy controls (HC, $n = 18$) watching an animated fearful face paradigm. To explore functional connectivity, we used independent component analysis (ICA) of fMRI data to characterize possible amygdala network alterations that may be caused by lateralized amygdala dysfunction. We furthermore investigated the relationship between activation within the amygdala network and ToM task performance. The pattern of amygdalar BOLD activation observed in response to an animated fearful face paradigm was bilateral amygdalar activation in HC and amygdala activation lateralized to the contralateral side in MTLE patients. In HC, a hemispheric asymmetry of the amygdala network was present with amygdala co-activation in predominantly left temporolateral and frontal brain structures. In MTLE patients, the observed asymmetry of amygdala connectivity was modulated by the side of pathology and the extent of amygdalar connectivity to the parahippocampal gyrus and insula was related to ToM test performance. These findings suggest that ipsilateral amygdalar dysfunction in MTLE is associated with alterations in remote temporal and frontal brain areas. The study of psychiatric and neurological disorders via network analysis allows for a shift of focus away from viewing dysfunctions of individual structures to a pathological network that possibly gives rise to a variety of symptoms.

Keywords Mesial temporal lobe epilepsy · Amygdala · fMRI · Functional connectivity · Theory of mind

Introduction

Patients with mesial temporal lobe epilepsy (MTLE) are at considerable risk of developing psychiatric problems such as affective mood and personality disorders [16]. The extent of structural lesions in the mesiotemporal lobes, epileptogenic activity, age at onset of seizures, and etiology are among the multiple factors that can influence psychopathology in MTLE. Furthermore, given the importance of the limbic system in emotion processing and social cognition, it is not surprising that epileptogenic lesions capable of disrupting limbic connectivity are associated with a great variety of clinically significant behavioral abnormalities [6, 7, 20, 29].

We have recently shown that ipsilateral amygdalar dysfunction is present in the majority of MTLE patients, illustrating that functional pathology includes the amygdala as revealed by BOLD functional magnetic resonance imaging (fMRI) [28]. The amygdala has extensive connections with various neocortical areas in the prefrontal cortex and anterior temporal lobe as well as subcortical

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structures [1, 3, 14, 27, 30, 31]. Considering these interconnections, the amygdala emerges as a nodal point in a network that links together cortical and subcortical brain regions considered to be critically involved in emotion processing [26].

In MTLE patients with hippocampal sclerosis, reductions in both functional and structural connectivity between hippocampal structures and adjacent brain regions have been reported [13, 19, 34], whereas little is known about the functional connectivity of the amygdala in unilateral MTLE. Using a region-of-interest (ROI) approach, Vuilleumier et al. [33] have shown that structural amygdalar lesions lead to deafferentation in extrastriate visual cortical areas. This is strong evidence that the amygdala is capable of modulating processes in functionally and anatomically distant parts of the brain [11].

The purpose of our study is to evaluate the relationship between ipsilateral amygdala dysfunction and remote temporal, frontal, and parietal brain structures, known to be closely interconnected with the amygdala. We used independent component analysis (ICA), a new data-driven method that allows one to image connectivity of significant nodes of activity [10]. We hypothesized that MTLE patients show an altered amygdala network depending on the lateralization of their epilepsies. Accordingly, left- and right-sided MTLE (LMTLE, RMTLE) patients were expected to show primarily impaired ipsilateral connectivity, whereas contralateral connectivity should be less affected.

Moreover, we investigate whether amygdala connectivity is related to theory of mind (ToM) abilities, which were assessed using the recognition of Faux Pas Test in which MTLE patients have previously been shown specifically to be impaired and which, among different validated tests, approved to be the most sensitive one for ToM deficits in MTLE [9, 29].

Materials and methods

Patients and healthy controls

A total of 28 consecutive patients with a diagnosis of unilateral medically refractory mesial temporal lobe epilepsy (MTLE) and unilateral hippocampal sclerosis, ipsilateral to epilepsy side (HS, 16 left-sided; 12 right-sided), admitted to the Swiss Epilepsy Centre between 2009 and 2010 were enrolled in this study (17 females; mean age 37.4 + 12.6 years; age range 16–60). Twenty-three patients were right-handed (self-reported), and fMRI indicated left-sided language dominance in all five left-handed patients. In all patients, the diagnosis of unilateral MTLE with partial and/or secondary generalized tonic–clonic seizures was based on typical clinical seizure semiology, interictal and ictal EEG findings, and the results of MRI scans (see Table 1).

All patients were therapeutically refractory to various first-line antiepileptic drugs (AEDs). None of the patients experienced a seizure in the 24-h period preceding the experimental session.

Eighteen right-handed (as assessed by the Edinburgh Handedness Inventory) [23], left-hemispheric dominant (as indicated by fMRI), native German-speaking participants with no history of psychiatric or neurological illness (confirmed by psychiatric clinical assessment) were enrolled (12 females; mean age 31.2 ± 5.8 years; age range 24–44). No abnormal findings on conventional brain MRI were observed in these controls.

The mean age of groups (MTLE, HC) did not differ significantly (ANOVA, n.s.), nor did gender distribution (Chi-square test, n.s.). LMTLE and RMTLE patients did

Table 1 Clinical data from MTLE patients

Patient	Side of seizure onset	Sex	Handedness	Age	Mean age at epilepsy onset in years	Duration of epilepsy in years
1	Left	w	RH	43	19	24
2	Left	w	RH	17	13	4
3	Left	m	RH	32	4	28
4	Left	m	RH	19	17	2
5	Left	w	RH	45	41	4
6	Left	w	RH	36	1	35
7	Left	w	RH	35	22	13
8	Left	m	RH	30	11	19
9	Left	m	RH	33	17	16
10	Left	m	RH	42	24	18
11	Left	w	RH	45	9	36
12	Left	w	LH	49	35	14
13	Left	w	RH	18	4	14
14	Left	m	LH	35	4	31
15	Left	w	LH	44	9	35
16	Left	w	RH	16	10	5
17	Right	w	RH	30	7	23
18	Right	m	RH	60	43	17
19	Right	w	RH	48	15	33
20	Right	m	RH	34	8	26
21	Right	m	RH	48	28	20
22	Right	m	LH	47	32	15
23	Right	m	RH	53	3	50
24	Right	w	RH	44	34	10
25	Right	w	RH	17	1	16
26	Right	w	LH	25	22	3
27	Right	w	RH	45	4	41
28	Right	w	RH	58	27	31