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Task activation and functional connectivity show concordant memory laterality in temporal lobe epilepsy

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ABSTRACT

Objective: In epilepsy, asymmetries in the organization of mesial temporal lobe (MTL) functions help determine the cognitive risk associated with procedures such as anterior temporal lobectomy. Past studies have investigated the change/shift in a visual episodic memory laterality index (LI) in mesial temporal lobe structures through functional magnetic resonance imaging (fMRI) task activations. Here, we examine whether underlying task-related functional connectivity (FC) is concordant with such standard fMRI laterality measures.
Methods: A total of 56 patients with temporal lobe epilepsy (TLE) (Left TLE [LTLE]: 31; Right TLE [RTLE]: 25) and 34 matched healthy controls (HC) underwent fMRI scanning during performance of a scene encoding task (SET). We assessed an activation-based LI of the hippocampal gyrus (HG) and parahippocampal gyrus (PHG) during the SET and its correspondence with task-related FC measures.
Results: Analyses involving the HG and PHG showed that the patients with LTLE had a consistently higher LI (right-lateralized) than that of the HC and group with RTLE, indicating functional reorganization. The patients with RTLE did not display a reliable contralateral shift away from the pathology, with the mesial structures showing quite distinct laterality patterns (HG, no laterality bias; PHG, no evidence of LI shift). The FC data for the group with LTLE provided confirmation of reorganization effects, revealing that a rightward task LI may be based on underlying connections between several left-sided regions (middle/superior occipital and left medial frontal gyri) and the right PHG. The FCs between the right HG and left anterior cingulate/medial frontal gyri were also observed in LTLE. Importantly, the data demonstrate that the areas involved in the LTLE task activation shift to the right hemisphere showed a corresponding increase in task-related FCs between the hemispheres.
Significance: Altered laterality patterns based on mesial temporal lobe epilepsy (MTLE) pathology manifest as several different phenotypes, varying according to side of seizure onset and the specific mesial structures involved. There is good correspondence between task LI activation and FC patterns in the setting of LTLE, suggesting that reliable visual episodic memory reorganization may require both a shift in nodal activation and a change in nodal connectivity with mesial temporal structures involved in memory.

1. Introduction

When evaluating the risk of surgery for temporal lobe epilepsy (TLE), the preservation of verbal and visuospatial episodic memory (EM) functions is of utmost importance [1]. To reach this goal, one must understand the brain regions subserving memory. An important first step in this process is identifying the hemispheric lateralization of memory processes. In the setting of TLE, this is particularly difficult, as there is an increased likelihood that cognitive functions have reorganized [2,3], rendering the normal assumptions about their localization or lateralization more tenuous. This is particularly true on an individual patient basis. As it is the nature and integrity of connections between brain nodes implementing memory, not just the nodes themselves, that influence memory representations and the probability of reorganization [4], it is important to identify if reorganization has occurred at the level of functional connectivity (FC), and then determine if there is a relationship between functional magnetic resonance imaging (fMRI) memory–task laterality and the FC underlying these laterality patterns. Investigations of episodic memory reorganization in TLE by our group [5,6] and others [7–12] have focused on the

Abbreviations: SET, scene encoding task; LI, laterality index; FC, functional connectivity.

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association between FC and visual or verbal EM functioning. No study, however, has incorporated task-related FC into tests of memory laterality and reorganization, going beyond the more standard and sole use of either task activation or resting FC as the basis for assessment in this group of epilepsies.

Given the newer surgical technologies being directed at more specific mesial regions for seizure freedom (e.g., thermal ablation), finer-grain knowledge of the functional integrity and reorganization potential of specific mesial regions becomes increasingly important, particularly in case of EM. Thus, as has been the case with other studies in this area [13–15], we will focus on mesial temporal subregions to determine if they display different patterns of EM lateralization.

Our primary research question is the following: are hemispheric asymmetries based upon activation during a fMRI visuospatial encoding task reflected in the underlying task-related FC? Consistent with prior literature demonstrating reorganization effects [5,6,15–18], we suspect that task activation will be stronger in the mesial regions contralateral to the seizure onset zone (SOZ) for both the parahippocampal and hippocampal gyrus (PHG, HG). Also, we predict that FC patterns will parallel task-activation memory encoding laterality patterns such that increased connections will occur contralateral to the SOZ compared to healthy controls (HCs). Our overarching goal was to better understand the factors that support adaptive reorganization of memory functions, all toward providing a more accurate assessment of the risk for memory deficits following surgical interventions for TLE. Unlike prior studies, the current study presents a unique and integrated approach highlighting the FC patterns that underlie task laterality during visual EM.

2. Material and methods

A total of 56 patients with drug-resistant unilateral TLE (31: left; 25: right) matched on age, handedness [19], and gender were recruited from the Thomas Jefferson University Comprehensive Epilepsy Center (Table 1). All the patients solely had temporal-lobe pathology, and all were recommended for anterior temporal lobectomy (ATL)/selective amygdalohippocampectomy (SAH) as treatment for their drug-resistant TLE. Details of the algorithm for surgical decision making are described in Sperling et al. [20]. A combination of video electroencephalography (EEG) (at least 96 h), magnetic resonance imaging (MRI), positron emission tomography (PET), and neuropsychological testing was used to localize the seizure focus. Expert board-certified neuroradiologists and epileptologists, by consensus decision, characterized and classified patients' neuroimaging findings and seizure type [21]. Patients were excluded from the study for any of the following: previous brain surgery, extratemporal/multifocal epilepsy, central nervous system illness other than epilepsy, contraindications to MRI, psychiatric diagnosis other than a depressive disorder, or hospitalization for any disorder listed in the Diagnostic and Statistical Manual of Mental Disorders-V. Depressive disorders were allowed given the high comorbidity of depression and epilepsy [22]. Patients were always assessed clinically before entering the scanner, and no patient was scanned if there was any sign or suggestion of a postictal state. As a policy, functional scans are canceled and rescheduled if the patient reports a seizure on the previous day or within a 24-hour period prior to the scan. Also, no patient had a seizure during the scanning procedure itself. A listing of individual patient pathology and other clinical information is now provided in the Supporting Information section (Supplemental Information, Table 1). Handedness was assessed using Edinburgh Handedness Inventory [19] by experienced neuropsychologists.

Thirty-four HCs were recruited to match the patient participants in age, gender, and handedness. All HCs were free of psychiatric or neurological disorders based on health screening measures. This study was approved by the Institutional Review Board for Research with Human Subjects at Thomas Jefferson University. All participants provided a written informed consent.

2.1. Scene encoding task (SET)

The preservation of visual–spatial memory (essential in the relational processing and encoding of nonverbal experiences and episodes) is an essential component in helping to maintain patients' quality of life [23]. We adapted and modified a scene encoding task [24] known to be a robust activator of bilateral mesial temporal lobe (MTL) structures such as the HG and PHG in both the patients with TLE and the HCs.

Table 1
Clinical and demographic characteristics of the experimental groups.

	RTLE HS-negative (13)	RTLE HS-positive (12)	LTLE HS-negative (16)	LTLE HS-positive (15)	Controls (34)	Stats (test, p value)
Gender (M/F)	7/6	3/9	8/8	7/8	18/16	0.46
Age (Years, M ± SD)	39.62 ± 14.38	44.74 ± 12.77	40.53 ± 15.82	41.03 ± 13.12	36.7 ± 12.6	0.81
Handedness (R/L)	10/3	10/2	12/4	15/0	31/3	—
Epilepsy Duration (Years, M + SD)	15.06 ± 11.20	17.36 ± 13.77	11.98 ± 10.03	26.95 ± 14.78*	N.A.	0.012*
Age at Onset (Years, M ± SD)	23.92 ± 12.54	27.25 ± 13.97	28.44 ± 14.80	14.03 ± 12.21*	N.A.	0.023*
Seizure Focality (without/with GTCS)	2/11	6/6	3/13	3/12	N.A.	0.15
Seizure Type	FIAS: 3 FIAS + GTCS: 8 FAS + FIAS + GTCS:2	FIAS: 4 FIAS + GTCS: 5 FAS + FIAS + GTCS:3	FIAS: 2 GTCS: 1 FIAS + GTCS: 7 FAS + FIAS: 2 FAS + FIAS + GTCS:4	FAS:1 FIAS: 2 GTCS: 1 FIAS + GTCS: 5 FAS + FIAS: 2 FAS + FIAS + GTCS:4	N.A.	—
Full scale IQ	99.64 ± 12.90	93.64 ± 15.73	94.57 ± 21.16	86.64 ± 15.44	N.A.	0.24
Scene encoding Task Accuracy	98.8%	99.6%	97.6%	97.5%	98.6%	—
Scene encoding Task Response Time (ms)	898 ± 388	756 ± 310	805 ± 166	829 ± 280	784	0.66
Medications (no. of patients)	2:Carbamazepine 4:Lamotrigine 1:Levetiracetam 1:Topiramate 1:Oxcarbazepine 3:Lacosamide 2:Other	2:Carbamazepine 4:Lamotrigine 1:Levetiracetam 1:Topiramate 2:Oxcarbazepine 4:Lacosamide 3:Other	1:Carbamazepine 4:Lamotrigine 4:Levetiracetam 0:Topiramate 0:Oxcarbazepine 8:Lacosamide 5:Other	1:Carbamazepine 6:Lamotrigine 9:Levetiracetam 0:Topiramate 3:Oxcarbazepine 4:Lacosamide 2:Other	N.A.	—

Abbreviations: RTLE = Right TLE; LTLE = Left TLE; FIAS = Focal Impaired Awareness Seizures; FAS = Focal Aware Seizures; GTCS = Generalized Tonic–Clonic Seizures; HS = Hippocampal sclerosis; ms = milliseconds.

* $p < 0.05$.