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Original Article

Reduced self-regulation of cerebrum contributes to executive impairment in patients with temporal lobe epilepsy

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Abstract: The aim of this study was to investigate the role of self-regulation of cerebrum in the executive impairment. 22 subjects were enrolled were assessed by a neuropsychological test of executive function using attentional networks test and the cerebral activity was evaluated by functional magnetic resonance imaging. The patients with TLE had a longer reaction time than controls ($P < 0.05$). Moreover, the healthy controls showed more right hemisphere lateralized activation in incongruent tasks. Finally, both positively and negatively correlated cerebral areas were found in the healthy controls but only negatively correlated cerebral areas were found in the TLE patients. Reduced cerebral lead to areas and lack of activation of right midline positively self-regulatory cerebral areas may executive impairment in TLE patients.

Keywords: FMRI, temporal lobe epilepsy, neuropsychological test, attentional networks test, executive function

Introduction

Temporal lobe epilepsy (TLE) is the most common focal epilepsy caused by abnormal epileptic discharges in temporal and limbic system. More and more studies have demonstrated that attentional and executive functions are impaired in TLE patients [1]. Temporal lobe epilepsy (TLE) is typically associated with long-term memory dysfunction. The frontal lobes support high-level cognition comprising executive skills and working memory that is vital for daily life functioning. Deficits in these functions have been increasingly reported in TLE. Evidence from both the neuropsychological and neuroimaging literature suggests both executive function and working memory are compromised in the presence of TLE. In relation to executive impairment, particular focus has been paid to set shifting as measured by the Wisconsin Card Sorting Task. Other discrete executive functions such as decision-making and theory of mind also appear vulnerable but have received little attention [2]. Zamarian et al found an important methodological issue as they suggest that executive function deficits in chronic mesial temporal lobe epilepsy may be individually variable and that their assessment should include different tests. Deficits in chronic mesial temporal lobe epilepsy are not limited to temporal lobe functions, such as memory, but may extend to extra temporal cognitive domains, such as executive functions [3]. Recent research indicates that longstanding temporal lobe epilepsy (TLE) is associated with extratemporal, i.e. parietal cortex damage. Weniger G expected that TLE patients with parietal cortex damage were impaired in the egocentric memory task [4].

Functional magnetic resonance imaging (fMRI) can be used to directly observe activities of certain brain regions and there were three attentional functions verified by neuroimaging: 1) alerting, i.e. maintaining the alert state, which involves the cortical projection of norepinephrine system; 2) orienting, which requires the selection of information from numerous senso-

ry inputs and involves temporal parietal junction, superior parietal lobe and frontal eye fields; and 3) execution, which involves resolution of conflicts between neural systems and regulation of thoughts and feelings. Markett S found robust statistical associations with centrality measures of global and local connectivity of nodes within the network with the alerting and executive control sub-functions of attention. The results provide further evidence for the functional significance of intrinsic connectivity networks and the hypothesized role of the fronto-parietal attention network [5]. Except for the neuroimaging, the neuropsychological tests are also applied to assess the executional function. Recently, research on attention has focused on 3 networks that are linked to separate brain regions, i.e. orienting, alerting, and executive control. The attention network test (ANT) is one of the methods to measure the three attention functions. However, neuropsychological investigations have not examined the anatomical disassociation of different attention networks with the same task. Comparing the brain damaged group with the normal controls, a reduced efficiency of the executive network was found in patients with frontal lobe and parietal lobe injuries, and there was also a deficit in the orienting network in patients with parietal lobe injuries. Analysis of lateralization indicated the right hemisphere superiority to the alerting system. The present study found that the three attentional networks were selectively impaired following brain damage, which affected different areas in the brain [6]. Dulay MF believes in patients with temporal lobe epilepsy, executive dysfunction is associated with depressed mood possibly reflecting disruption of cortical-limbic pathways and/or frontal-striatal circuitry [7]. The attentional network test (ANT) provides a survey of efficiencies of alerting, orienting and executive networks. ANT performs a more reliable survey than traditional methods because of its objective design, good operability and repeatability. It has been used to detect attentional impairments in children with idiopathic generalized epilepsy. Federico et al developed a variant of this test to examine attentional effects in response to stimuli with and without social-cognitive content. Fish, drawings or photographs of faces looking to the left or right were used as target stimuli. Results collected from twenty-four university students showed that photographs of faces positively affected attentional orienting and executive control, whereas reduced the efficiency of alerting, as compared to both face drawings and fish. These results support the status of human faces as a special class of visual stimuli for the human attentional systems [8]. Rzezak et al found children with temporal lobe epilepsy had worse performance in focused attention, immediate and delayed recall, phonological memory, mental tracking, planning, and abstraction. Planning, abstraction, and mental tracking were correlated with visual and verbal memory. Children with severe executive dysfunction had worse performance in verbal and visual memory and learning tests. This study showed that executive dysfunction was related to memory performance in children with temporal lobe epilepsy [9]. Longo et al do the research about children with frontal lobe epilepsy and temporal lobe epilepsy. The study shows youth with frontal lobe epilepsy had significantly greater difficulty on the Wisconsin Card Sorting Test compared to the temporal lobe epilepsy group. Both of them performed significantly below the normative sample levels on attention and working memory tasks. As a whole, it appears that some, although not all, executive dysfunction is specific to frontal lobe epilepsy [10]. Hence, with the combination of ANT and fMRI, we can explore visually the brain abnormality caused by TLE. Our study aimed to study the correlation between behavioral performance and fMRI in TLE patients.

Methods

Subjects

Eleven right-handed patients were recruited from the first affiliated hospital of Guangxi Medical University. Epilepsy was diagnosed based on diagnostic scheme of the International League Against Epilepsy (2001). The criteria for TLE were: 1) clinical symptoms suggested that epileptic foci was located in temporal lobe; 2) EEG during exacerbation or inter-exacerbation showed epileptic foci in temporal lobe; 3) hippocampus sclerosis or atrophy was detected by MRI neuroimaging scans19; 4) disciplined in taking anti-epileptic drugs and had no seizures within one month; 5) scored higher than 24 in simple intelligence scale; 6) without other serious physical illness; 7) without visual and linguistic disability; 8) without drug abuse, i.e. irregular use of antiepileptic, antipsychotic, tri-

cyclic and monoamine oxidase inhibitors within last 6 weeks; 9) consent and cooperation; and 10) having not received similar tests. Controls were 11 right-handed healthy volunteers matched in education, gender and age. The trial was conducted in compliance with current Good Clinical Practice standards and in accordance with the principles set forth under the Declaration of Helsinki (1989). An informed consent was obtained from each patient and approved by Local Ethic Committee.

Experimental task

The ANT test was done according to the previous researches. Briefly, during the test, the subject was required to put his thumbs on response box keys and press them with his left hand or right hand following onscreen prompts. The stimulus was presented against a gray background and back-projected onto a screen that the subject viewed through a mirror located on the scanner's head coil. E-Prime software (www.pstnet.com/eprime) was applied to the block-designed fMRI. The designed paradigm was a 30 s task block followed by a 30 s rest block. For the 30 s task block, a star stimuli cue was presented at the center of the screen for 200 ms, then was changed into target stimuli signal. The subject was required to press the key immediately when the target signal occurred. The target signal lasted 1800 ms and the task would repeat. The target stimuli signal of task-block consists of congruent tasks and incongruent tasks. A stimulus consisted of a row of 5 horizontal black lines with arrowheads pointing leftward or rightward. The target was a leftward or rightward arrowhead at the center. This target was flanked by two arrows in the same direction (congruent condition) or in the opposite direction (incongruent condition). The participants' task was to identify the direction of the central arrow by pressing one key for left direction and a second key for right direction. Congruent and incongruent conditions occurred twice each. Control condition lasted 30 ms by showing a central "+" on the screen. The control block was a 30 s rest block presenting only black crosshair fixation in the center of the screen. Each cycle consisted of a control block and a task block (congruent condition/incongruent condition). Four task blocks of congruent and incongruent stimulus were presented in each of two runs, totaling four cycles. 240 s were used to complete the fMRI scanning session. Behavioral practice by ANT was required before fMRI scanning.

MRI data acquisition

MRI studies were performed on a 3.0T Philips Intera Achieva scanner (Philips Medical Systems, Best, Netherlands). Medical SAMRTEC SA-980 (Shenzhen Medke Technology Co. Ltd, Shenzhen, PR China) visual presenting system was used to present stimulus. Anatomic images were acquired using a T1-weighted three-dimensional turbo field-echo sequence of 130 transverse slices of 1 mm thickness (repetition time (TR) = 60 ms, echo time (TE) = 16 ms, field of view (FOV) = 220 × 220 mm^2). Functional imaging used a gradient-echo and echo planar imaging sequences (22 slices of 5.0 mm thickness; TR = 2000 ms; TE = 30 ms; slice gap = 1 mm; FOV: 220 × 220 mm^2 flip angle: 90°). The hippocampus volumes were defined as the median of two values measured by a neurologist and radiologist respectively at General Electric Co (GE) Workstation 4.2. fMRI Data was analyzed with Statistical Parametric Mapping software (SPM2, Welcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm/). Spatial pre-processing, model specification and parameter estimation were performed. A two-level random-effect analysis was employed. The first 5 volumes of fMRI data were discarded to remove saturation effects. The spatial pre-processing included realignment of head motion, adjustment of the images to match the structure image, normalization to the standard MNI (Montreal Neurological Institute) template and spatial smoothing with a Gaussian kernel of 8 × 8 × 8 mm^3 full-width at half-maximum (FWHM). By applying the General Linear Model (GLM) 21, an image file was automatically generated for group analysis (or random-effects analysis). And cluster size was of 10 voxels.

Data analysis

SPSS 13.0 was used for statistical analysis. $P < 0.05$ was set for the significant level. Quantitative data was presented as $\chi \pm s$; and independent samples t-test was employed to analyze reaction time. T test was performed on the data from evoked brain regions when congruent and incongruent tasks were required within the group or between groups.

Table 1. Demographic and Clinical Characteristics of TLE

Subject	Age	Gender	Handed-ness	Onset Age	Type of Seizure	MRI Findings	Syndrome of epilepsy	MMSE	Antiepileptic Drugs	History of-Febrile Convulsion	Hippocampus Volume ▲cm^2	
											Left	Right
1	22	Female	Right	19	CPS	Right HA	Right TLE	28	CBZ Clonazepam	+	2.75	2.3
2	24	Male	Right	21	CPS GTCS	Right HA	Right TLE	27	CBZ VPA	+	2.52	1.74
3	25	Male	Right	18	CPS	Right HA	Right TLE	30	CBZ LVT	-	2.85	1.93
4	19	Male	Right	14	CPS GTCS	Right HS	Right TLE	28	CBZ VPA	+	3.21	2.65
5	18	Female	Right	16	GTCS CPS	Right HA	Right TLE	26	CBZ VPA	-	2.73	2.6
6	22	Male	Right	15	CPS GTCS	Right Lateral Temporal AVM?	Right TLE	27	CBZ VPA PHT	-	2.78	2.91
7	20	Male	Right	18	CPS	Right HA	Right TLE	30	CBZ	-	2.91	2.2
8	23	Male	Right	15	CPS GTCS	Right HS	Right TLE	29	VPA CBZ	-	2.81	2.68
9	53	Female	Right	40	GTCS CPS	Bilateral HS	Bilateral TLE	25	CBZ	-	2.82	2.91
10	20	Female	Right	15	CPS	Right HA	Right TLE	30	CBZ LVT	-	2.76	2.51
11	21	Male	Right	19	CPS	Right HA	Right TLE	28	CBZ LVT	+	2.9	2.67

CPS: complex partial seizure; GTCS: generalized tonic-clonic seizure; HS: hippocampus sclerosis: HA: hippocampus atrophy; AVM; arteriovenous malformation; CBZ: carbamazepine; LVT: levetiracetam; PHT: phenytoin; Clonazepam; *Patients' fMRI see **Table 2**; ▲TLE: hippocampus volume of left and right sides shows significant difference $P < 0.05$, $t = 3.4$.

Table 2. One-sample t-test showing fMRI activation peaks for the main effects of performing incongruent task to congruent condition task within TLE and controls

Subjects	Z-score	*P* value	Coordinates MIN space			Anatomical Region	Voxel
			X	Y	Z		
HC: Incongruent > Congruent	3.92	0.000	58	-6	-32	Right inferior temporal gyrus	72
	3.64	0.000	28	-36	8	Right hippocampus	13
	3.12	0.001	-52	-74	28	Left inferior temporal gyrus	49
	3.11	0.001	4	-54	26	Right posterior cingulated gyrus quadrate gyrus	131
	3.03	0.001	18	62	10	Right superior frontal lobe	14
	3.02	0.001	38	-72	38	Right parietal lobe	26
TLE: Incongruent > Congruent a	NSb	NS					
	2.93	0.002	18	38	12	Right prefrontal lobe	53
	2.81	0.002	16	-30	53	Right frontal lobe	34
	2.79	0.003	-36	14	-32	Left superior temporal lobe	23
	2.74	0.003	12	-46	-38	Right anterior cerebellum	26

Incongruent > Congruent: brain regions that show remarkable active when 5 arrows in the opposite direction (incongruent) VS arrows in the same direction (congruent); NS: not significant; MNI: Montreal Neurological Institute; a: the significant level was $P < 0.001$; b: the significant level was $P < 0.01$.

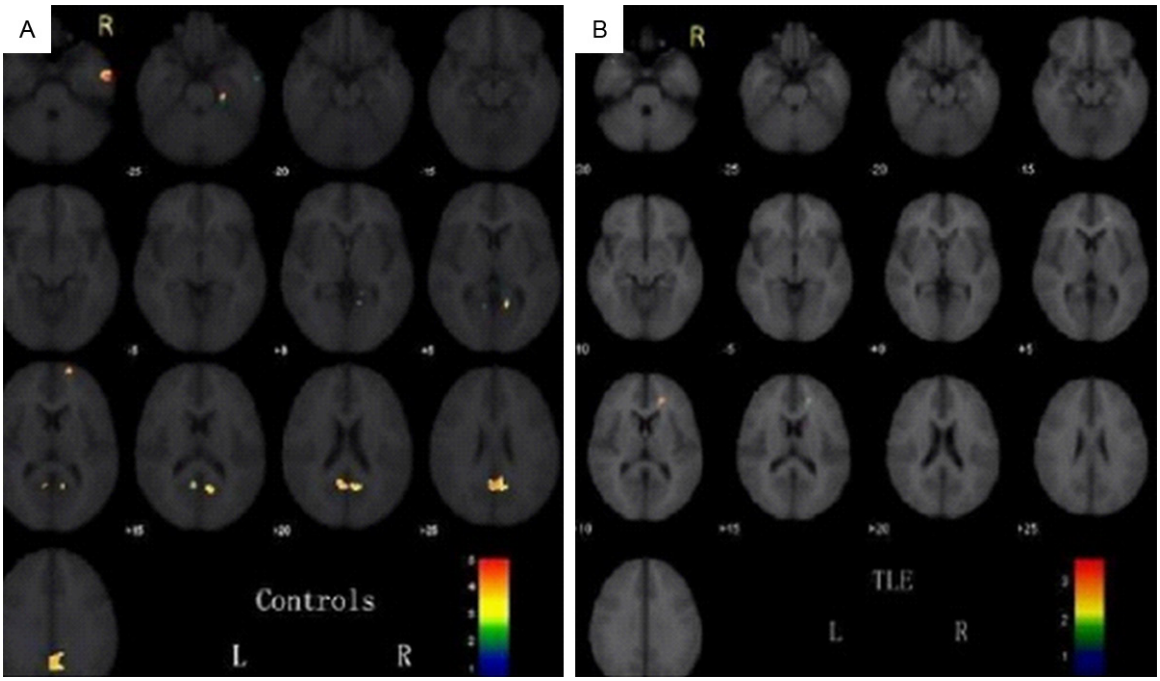

Figure 1. Main effect of performing in the incongruent task compared with congruent task in control and patients with TLE. Color scale indicates t-values. A: The right hemisphere lateralized activation in control (> 10 voxels, $P < 0.001$). B: Images showed only right prefrontal and right parietal lobe activation were found in patients with TLE (> 10 voxels, $P < 0.01$).

Results

Clinical characteristics and behavioral evaluation

There were no significant differences of age, gender distribution and MMSE scores between TLE patients and healthy controls. All the patients have complex partial seizures and six patients accompanied with generalized tonic-clonic seizures. All the patients have right hippocampus atrophy or sclerosis and one patient have bilateral hippocampus atrophy. An interesting finding was that the patients who have bilateral hippocampus atrophy had bilateral TLE. And there was a less volume of right hippocampus than left hippocampus in TLE patients (2.46 ± 0.38 vs. 2.82 ± 0.17, $P < 0.05$). The demographic and clinical characteristics of TLE patients were listed in **Table 1**. Reaction

Table 3. Two sample t-tests showing interactions between patients and controls

Subjects	Z-score	*P* value	Coordinates MIN space			Anatomical region	Voxel
			X	Y	Z		
TLE < HC	3.94	0.000	-26	-84	-34	Left cerebellum peduncle	18
	3.87	0.000	-52	-70	28	Left meditemporal gyrus	57
	3.84	0.000	18	62	8	Right inboard prefrontal	14
	3.49	0.000	6	-48	28	Right posterior cingulated gyrus	26
	3.47	0.000	2	-66	28	Right parietal lobe	66
TLE > HC	Ns	Ns					

Table 4. Simple regression analysis between the executive function reactive time and fMRI image files of two groups

	Subjects	Z value	*P* value	MIN coordinate space			Anatomical location
				X	Y	Z	
Negative correlation analysis	Healthy Volunteers	4.03	0.001	-39	-92	-18	Left inferior occipital gyrus (BA18)
		3.49	0.001	-16	48	-24	Left middle frontal gyrus (BA11)
		3.41	0.001	4	58	-6	Right medial frontal gyrus (BA10)
	TLE	NS					
Positive correlation analysis	Healthy control	4.01	0.001	-20	-38	76	Left posterior gyrus
		3.8	0.001	44	-2	16	Right insula
		3.68	0.001	-8	-34	8	Callus
		3.5	0.001	-26	32	8	Left frontal lobe
	TLE	4.55	0.001	54	30	28	Right middle frontal lobe
		3.89	0.001	-40	24	-6	Left inferior frontal lobe
		3.8	0.001	40	24	-14	Right inferior lobe
		3.75	0.001	4	22	52	Right mediate frontal lobe

NS: not significant; MNI: Montreal Neurological Institute; *P* value < 0.001; BA: Brodmann area.

times in ANT of TLE patients (158.9 ± 50 ms) were significantly prolonged compared to controls (112.4 ± 28.3 ms, $P < 0.05$).

fMRI activation

Activation peaks in participants and their interactions across groups are given in **Tables 2** and **3**. Significant difference of activation regions was found within healthy controls performing incongruent and congruent tasks: lateralization was found in right inferior temporal gyrus, right hippocampus, right prefrontal lobe and the posterior of cingulate gyrus. In contrast, only when significant level P was set at 0.01, limited and small evoked brain region activities in prefrontal brainstem and anterior cerebellum could be detected in the right hemisphere.

Brain region activation

The healthy controls showed right hemisphere lateralized activation when performing incongruent tasks compared with congruent tasks (**Table 2** and **Figure 1**). Activation was mainly seen in the right inferior temporal gyrus, right hippocampus, right cingulate gyrus precuneus, right superior frontal gyrus and precuneus of right parietal lobe. However, there was no significant difference between performing incongruent tasks and performing congruent tasks in the TLE group (**Table 2** and **Figure 1**). For group comparisons (**Table 3**), there were less remarkable activations in TLE group compared with healthy controls ($P < 0.05$).

Correlation analysis

SPM simple regression between reactive times and fMRI activities were performed. For healthy controls, left occipital lobe and frontal lobe had negative correlations with reaction time while there was no significant difference in TLE patients (**Table 4**). Posterior-gyrus of left parietal lobe, right insula, corpus callosum and cortical and subcortex of left frontal lobe had posi-

tive correlations with reaction time ($P < 0.001$, **Table 4**) in healthy controls. And this positive correlation was also observed for brain regions including cortex and subcortex structure of right middle frontal gyrus, inferior frontal gyrus and medial frontal gyrus in TLE patients (**Table 4**).

Discussion

Executive function involves a complex network in the brain

The brain areas for executive function were thought to be located in prefrontal lobe and parietal lobe. Our data also suggested activation of midline regions of prefrontal lobe closed to the anterior cingule gyrus and parietal lobe in healthy controls. However, in conflict tasks such as ANT, cerebral activation had a tendency of involving the right hemisphere. Not only anterior cingulate and midline prefrontal lobe but also temporal, parietal lobes and posterior cingulate were involved in executive function among healthy participants in our study. These areas could be activated respectively and implement attentional function collaboratively by focusing on different substantial tasks. Performance in executive function was normal even with damage in anterior cinglue gyrus. It indicates that attentional function is not merely related to a single brain region but a complex network composing series of relevant brain regions. Participants (N = 125) were tested with the Lateralized Attention Network Test that allowed us to investigate the efficiency of the networks in both visual fields. Asanowicz et al found a lateralized visual fields advantage when a target occurred in an unattended location, which seems to reflect right hemisphere superiority in control of the reorienting of attention. Furthermore, a lateralized visual fields advantage in conflict resolution was observed, which may indicate hemispheric asymmetry of the executive network. No visual fields effect for alerting was found. The results, consistent with the common notion of general right hemisphere dominance for attention, provide a more detailed account of hemispheric asymmetries of the attentional networks than previous studies using the Lateralized Attention Network Test task [11]. Petersen and Posner update 1990 Annual Review of Neuroscience article, "The Attention System of the Human Brain". The framework presented in the original article has helped to integrate behavioral, systems, cellular, and molecular approaches to common problems in attention research. The framework has been both elaborated and expanded in subsequent years. Research on orienting and executive functions has supported the addition of new networks of brain regions [12].

Executive function impairment was detected by behavioral tests in TLE patients

Roca et al obtained results suggest that the proposed new test (ANTI-Vigilance or ANTI-V) is useful to achieve a direct measure of vigilance and could be considered as a new tool available in cognitive, clinical or behavioural neurosciences for analyzing vigilance in addition to the usual ANT scores [13]. Our study showed that TLE patients had significant prolonged reaction time in ANT test. It was in consistence with previous researches which showed 56% of mesial TLE patients had impaired sorting ability on the WCST, with 30% of them showing severe impairment of executive functions 2. This indicates that TLE patients might have difficulty in resolving conflicting tasks. However, our present study did not detect any significant difference of MMSE scores between TLE patients and healthy controls. This may be caused by evaluated tools or population and it need further studies to confirm it. Hudson JM believed impairments in attentional control in TLE tend to be selective. The greatest deficits appear to be on tasks that invoke a high level of processing resources. In contrast, sustained attention is less compromised and the capacity to allocate cognitive resources appears to be normal in patients with TLE [14].

Less fMRI activation in TLE patients

Since right hemisphere is tightly correlated with executive function, which was impaired in TLE patients, we used fMRI to find which brain area was insulted in TLE patients. TLE patients exhibited significantly less activation than healthy controls in the right prefrontal lobe, right posterior cingulated, right parietal lobe, left cerebellum peduncle and left posterior medial temporal gyrus regions. These findings suggested that deficits in the attentional executive functions in TLE patients were related to abnormal activities in frontal, parietal and other regions that are involved in resolving conflicting attentional executive processes. Therefore,

another question was proposed which was whether there was correlation between behavioral tests and fMRI data. Tuchscherer et al found the temporal lobe epilepsy had lower baseline thalamic volumes than controls and also performed more poorly on measures of executive functioning. Total thalamic volume significantly predicted subsequent performance on all three measures of executive function [15]. Executive functions are processes that act in harmony to control behaviors necessary for maintaining focus and achieving outcomes. Executive dysfunction in neuropsychiatric disorders is attributed to structural or functional pathology of brain networks involving prefrontal cortex (PFC) and its connections with other brain regions. The PFC receives innervations from different neurons associated with a number of neurotransmitters, especially dopamine (DA). Bowirrat et al review findings on the contribution of PFC DA to higher-order cognitive and emotional behaviors [16]. The present study suggests that alterations of the dopaminergic system result from epileptic activity and could be involved in the physiopathology of TLE and the comorbid anxiety and depression [17]. Functional magnetic resonance imaging (fMRI) can accurately reflect the hemodynamics and functional activities in certain regions of the brain. Zheng et al data indicate that despite neuropsychological test performance is normal; the alerting network is deficient in the TLE patients. The decreased activation of brain regions of right occipital lobe, cerebellum, right frontal lobe, brain stem and temporal lobe may be the neural basis of altering network impairment in TLE patients [18].

The correlation analysis between behavioral tests and fMRI results

The correlation analysis revealed that there were both positive and negative correlations between fMRI activities and reaction times in healthy controls. TLE patients only showed positive correlations. Not only anterior cingulate and midline prefrontal lobe but also temporal, parietal lobes and posterior cingulate affected the activation of executive functions among healthy participants. Reduced activation and deficiency of positive self-regulation in cerebral areas may cause executive impairment in TLE patients. Some limitations of our study: 1) relatively small samples, we only included 11 TLE patients and the same amount of healthy controls. Further studies need more patients and controls to drive the conclusion. 2) Operational functions of some complicated cognitive tasks might be interfered in patients with long-term anti-epileptics administration 30? Further study with patients without anti-epileptics administration would lead to more accurate result; and 3) patients in our study all had right side lesion. Further study of patients with left hippocampal lesion would lend more insight into the relation between operational function and the position of lesion. Campo et al measured magnetoencephalographic responses during verbal working memory encoding in left mesial temporal lobe epilepsy patients and controls, and compared their effective connectivity within a frontotemporal network using dynamic causal modelling. Critically, a negative correlation was observed between these changes in patients, with decreases in ipsilateral coupling among temporal sources associated with increases contralateral frontotemporal interactions. Furthermore, contralateral frontotemporal interactions were inversely related to task performance and level of education. The results demonstrate that unilateral sclerosis induced local and remote changes in the dynamic organization of a distributed network supporting verbal WM. Crucially, pre- (peri) morbid factors (educational level) were reflected in both cognitive performance and (putative) compensatory changes in physiological coupling [19]. Sidhu et al [20] did a research about a functional magnetic resonance imaging study mapping the episodic memory encoding network in temporal lobe epilepsy. Correlational analysis showed that patients with right hippocampal sclerosis with better visual memory activated the amygdala bilaterally, right anterior parahippocampal gyrus and left insula. Right sided extra-temporal areas of reorganization observed in patients with left hippocampal sclerosis during word encoding and bilateral lateral temporal reorganization in patients with right hippocampal sclerosis during face encoding were not associated with subsequent memory formation. Reorganization within the medial temporal lobe, however, is an efficient process. The orbitofrontal cortex is critical to subsequent memory formation in control subjects and patients. Activations within anterior cingulum and insula correlated with better verbal and visual subsequent memory in patients with

left and right hippocampal sclerosis, respectively, representing effective extra-temporal recruitment.

Conclusion

In conclusion, reduced activation and deficiency of positive self-regulation in cerebral areas may cause executive impairment in the patient with TLE.

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Disclosure of conflict of interest

None.

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