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Impaired prefrontal cortex-thalamus pathway in intractable temporal lobe epilepsy with aberrant executive control function: MRI evidence

Chao Zhang [a,b,c,1], Haiyan Zhang [d,1], Kai Xu [c], Hongyu Yang [a,b], Chang Liu [e], Tao Yu [e], Nan Chen [a,b,*], Kuncheng Li [a,b,*]

[a] Department of Radiology, Xuanwu Hospital, Capital Medical University, Beijing, PR China
[b] Beijing Key Laboratory of Magnetic Resonance Imaging and Brain Informatics, Beijing, PR China
[c] Department of Radiology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu Province, PR China
[d] Department of Radiology, Affiliated 2 Hospital of Xuzhou Medical University, Xuzhou, Jiangsu Province, PR China
[e] Department of Functional Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, PR China

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HIGHLIGHTS

- The dorsolateral prefrontal cortex (DLPFC)-thalamus pathway is altered in temporal lobe epilepsy patients with impaired executive control function (ECF).
- The DLPFC-thalamus pathway has consistent enhancement ipsilaterally to the epileptogenic focus.
- ECF performance is not correlated with connectivity alterations of the DLPFC-thalamus pathway.

ABSTRACT

Objectives: This study aimed to assess structural and functional connectivity alterations of the prefrontal cortex (PFC)-thalamus axis in individuals with unilateral intractable temporal lobe epilepsy (TLE) showing executive control function (ECF) impairment and to explore the potential mechanism.
Methods: Thirty-eight individuals with intractable left TLE and twenty-nine healthy controls (HCs) were recruited for diffusion tensor imaging (DTI) and resting-state fMRI (rs-fMRI) scanning. According to the ECF state, patients were assigned to normal and impaired ECF groups. Functional connectivity (FC) and probabilistic diffusion tractography of the PFC- thalamus pathway were assessed. The general linear model (GLM) was employed for comparing fiber number (FN) and FC between groups. Pearson correlation analysis of FC, FN and ECF test scores was performed.
Results: FC and FN of left DLPFC-thalamus pathway were significantly increased in the impaired ECF group compared with the normal ECF and HC groups. However, FC and FN were not correlated with ECF score.
Conclusions: These findings indicated increased connectivity between DLPFC and the ipsilateral thalamus might reflect nonfunctional nerve remodeling along the seizure pathway.
Significance: The present findings suggest that the DLPFC-thalamus pathway may be an important structure for exploring the mechanisms of TLE with ECF dysfunction.

1. Introduction

Executive control function (ECF) impairment in temporal lobe epilepsy (TLE) has been increasingly reported (Martin et al., 2000; Kim et al., 2007), and can cause patients to lose the ability of managing daily life while imposing a heavy burden to families and the society (Lin et al., 2012). However, the mechanisms underlying TLE with ECF dysfunction remain unclear.

* Corresponding authors at: No. 45, Changchun Street, Xicheng District, Beijing, PR China.
E-mail addresses: chenzen8057@xwhosp.org (N. Chen), likuncheng@xwhosp.org (K. Li).
[1] Contributed equally to this work.

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The reasons why ECF deficits occur in TLE are inconsistent according to previous reports. Earlier studies reported ECF decrease in TLE cases may result from hippocampal function involvement in interactions or new information registration (Giovagnoli, 2001). Results from rs-fMRI studies also suggested that the hippocampus is the crucial structure in TLE with impaired ECF (Ji et al., 2013). However, others found no association of the hippocampus with ECF measurement in TLE cases (Hermann and Seidenberg, 1995a; Martin et al., 2000). Our previous study demonstrated that unilateral TLE was associated with functional integration beyond the diseased temporal lobe (Zhang et al., 2017). In addition, effective resection of epileptogenic foci does not prevent ECF decline in patients with TLE acquiring a seizure free status after surgery (Cleary et al., 2013).

A voxel-based morphometry (VBM) study indicated DLPFC atrophy predominantly accounts for ECF impairment in TLE with hippocampal sclerosis (HS) (Di Rienzo et al., 2014). Subsequent findings indicate that PFC is an important hub in the circuit subserving ECF performance (Wang et al., 2007). Specifically, many studies consistently pointed out that the thalamus is an important structure interacting with PFC, accounting for ECF performance in TLE (Leach et al., 2006; Martin et al., 2017).

The PFC and the thalamus cannot be dissociated in normal human cognitive function (Vermeulen and Aldenkamp, 1995; Schoeler et al., 2014). An anatomical study found numerous white matter connections between the frontal lobe and the thalamus (Holmes et al., 2014), which constitute the basal structure of the PFC-thalamus pathway (Nomura et al., 2010; Crittenden and Mitchell, 2015). A recent study assessing patients with Lennox-Gastaut syndrome found enhanced functional connectivity (FC) strength in thalamocortical circuits (Warren and Abbott, 2017). Increased FC between the PFC and the thalamus was also observed in TLE patients with short-term memory deficits (Voets et al., 2015). Furthermore, abnormal structure connectivity of the PFC-thalamus pathway is closely correlated with ECF impairment in schizophrenia (Orellana and Slachevsky, 2013). It is notable that the frontal cortex shows a pathological covariation with the thalamus in TLE, which is caused by seizure propagation across these two structures (Hetu et al., 2013). These findings support the hypothesis that the PFC–thalamus pathway may be an important structure for exploring ECF impairment in TLE.

Currently, a limited number of studies have assessed the role of DLPFC-thalamus pathway alterations in TLE with impaired ECF. The present study firstly combined resting-state functional magnetic resonance image (rs-fMRI) and diffusion tensor imaging (DTI) to characterize the DLPFC-thalamus pathway in TLE patients with ECF deficits. Previous reports indicated that patients with left TLE are more likely to develop ECF disorders than the right one (Horel, 1994; Winston et al., 2013). In this study, we focused on the patients with left TLE. First, we assessed whether unilateral TLE patients with ECF impairment have functional and structural connectivity alterations in the DLPFC-thalamus pathway. Secondly, the association of functional and structure connectivity with Wisconsin Card Sorting Test (WCST) score, which measure ECF ability quantitatively, was evaluated. Simultaneously, we observed whether structure and resting-state functional connectivity had the same pattern of alterations. We hypothesized that the DLPFC-thalamus pathway plays an important role in TLE patients with abnormal ECF.

2. Materials and methods

This study had approval from the Ethics Committee of Xuanwu Hospital, Capital Medical University, Beijing, China. All participants provided signed informed consent according to the Declaration of Helsinki.

We consecutively included 38 patients with TLE (29 HS and 9 neocortical TLE cases) with intractable left TLE diagnosed by comprehensive presurgical assessment and postsurgical pathological data (Table 1).

WCST is considered the "gold standard" for ECF assessment, and widely employed in chronic TLE reports (Martin et al., 2000; Royall et al., 2002; Kim et al., 2007). According to our previous study, we employed commonly used parameters of WCST to test ECF performance of all subjects, which included response error (RE), perseverative response (RP), perseverative error (RPE), non-perseverative error (NRPE), and categories completed (CC) (Fig. 1) (Kim et al., 2007; Gandy et al., 2016; Zhang et al., 2017). Normal ECF was reflected by all 5 WCST sub-scores within acceptable ranges; otherwise, ECF impairment was considered. The normal range was based on the T-score of RP, with the final value below 30 (Kim et al., 2007; Gandy et al., 2016). According to WCST testing, patients were divided into normal (N = 18; 11 males and 7 females; 26.8 years old averagely [13–42 years]; education years averaging 10.3 [4–15 years]) and impaired (N = 20, 11 males and 9 females; 26 years old averagely [13–38 years]; education years averaging 10.0 [4–16 years]) ECF subgroups. The patients received routine therapy, without any additional relevant treatment; age at seizure onset and seizure duration were similar between the normal and impaired ECF groups (Table 1). No patient showed extra-temporal lobe lesions. Twenty-nine healthy controls (13 males and 16 females; 27.4 years old averagely [23–35 years]; education years averaging 11.9 [5–19 years]) were assessed as the healthy control (HC) group, undergoing identical neuropsychological examinations. Age, gender distribution, and education level were

Table 1
Patient characteristics.

Variable	G1 (N = 18)	G2 (N = 20)	HC (N = 29)	Between-group comparisons (p values)		
				G1 vs G2	G1 vs HC	G2 vs HC
Gender (M/F)	11/7	11/9	13/16	0.543[a]		
Age (years)	18–42	18–38	23–35	0.795[a]		
	27.7 ± 7.1	26.6 ± 5.7	27.4 ± 3.7			
Edu (years)	4–15	4–16	5–19	0.159[a]		
	10.3 ± 2.9	10.0 ± 3.5	11.9 ± 4.0			
Age at seizure onset	3–30	4–24	N/A	0.884	N/A	N/A
	11.2 ± 7.2	10.8 ± 6.1	N/A			
Duration of TLE	8–36	4–34	N/A	0.831	N/A	N/A
	15.6 ± 6.9	15.1 ± 7.7	N/A			

M, male; F, female; Edu, education; MoCA, Montreal Cognitive Assessment; IQ, intelligence quotient; G1, normal ECF; G2, impaired ECF; HC, healthy control; N/A, not applicable.
Data are range and mean ± SD.
[a] Comparison of the three groups.

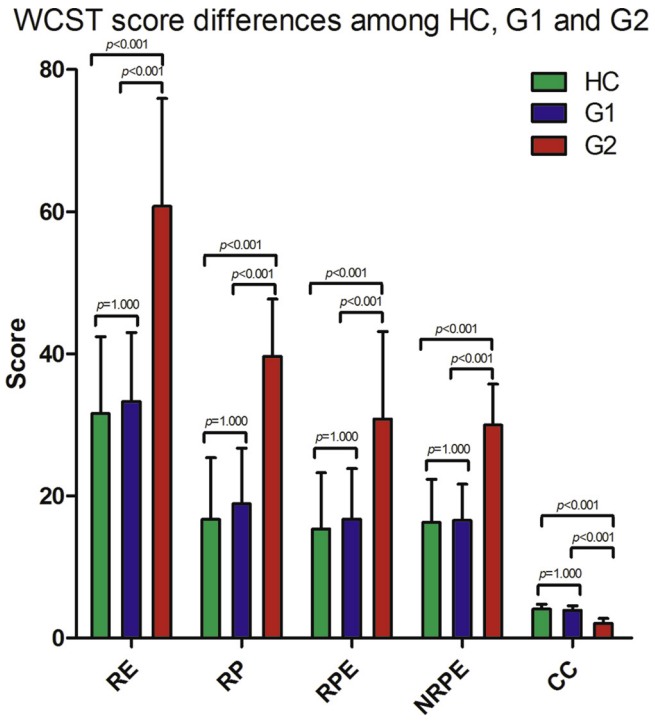

Fig. 1. Intergroup difference of WCST tests among HC, G1 and G2. Significant differences of WCST scores of RE, RP, RPE, NRPE and CC was found among HC, G1 and G2 ($p < 0.001$). No significant difference of these five parameters was found between HC and G1 ($p = 0.000$). CC, categories completed; G1, normal ECF group; G2, impaired ECF group; RE, response errors; RP, perseverative responses; RPE, perseverative errors; NRPE, nonperseverative errors.

similar between HCs and patients (Table 1). All participants underwent the same MRI scanning protocol.

2.1. MRI procedure

A 3.0T Magneton Trio Tim MRI scanner (Siemens Healthcare, Germany) equipped with a 32-channel phase-array head coil was employed for all individuals. Head motion was minimized, as well as imaging noise. Patients were advised to remain calm, with eyes closed and smooth breathing, avoiding thinking of any specific thing. Routine brain axial fluid-attenuated inverse recovery (FLAIR) sequence scanning was first performed to rule out other cerebral abnormalities. Then, T1-weighted imaging using 3D-MP-RAGE (three-dimensional magnetization-prepared rapid gradient-echo) were performed to acquire isotropic voxels of 1 mm × 1 mm × 1 mm (3D brain structure imaging). The DTI series used 64 directions (TR = 9500 ms, TE = 90 ms, matrix = 128 × 128, FOV = 256 mm), with individual volumes consisting of 70 contiguous 2 mm slices at 2 mm × 2 mm × 2 mm resolution. Resting BOLD imaging was carried out with an echo-planar sequence as follows: time of repetition/time of echo = 2000/30 ms, field of view = 220 mm × 220 mm, slice thickness = 3 mm, voxel size = 3.4 mm × 3.4 mm × 3.0 mm, slice number = 35, flip angle = 90°, and volume number = 180).

2.2. Seeds of the DLPFC-thalamus pathway

The DLPFC comprises Brodmann's areas (BAs) 9 and 46; the bilateral DLPFC was selected based on the BA template. The bilateral thalamus was identified using the anatomical Automatic Labeling (AAL) template (Fig. 2).

2.3. DTI tractography of DLPFC-thalamus pathway

Digital Imaging and Communications in Medicine (DICOM) images were processed on a Linux workstation. Next, eddy current distortion and motion artifacts in the DTI dataset underwent correction with FMRIB's Diffusion Toolbox (FDT) (FSL v5.0.1; United Kingdom; http://fsl.fmrib.ox.ac.uk/fsl). Brain extraction was performed using the brain extraction tool (BET) (Martin et al., 2017), and a binary brain mask was generated in this process. We employed affine (12 parameter model) registration of 64 diffusion volumes to images without diffusion weighting with FMRIB's Linear Image Registration Tool (FLIRT) to further improve data quality (Klein et al., 2014). The BEDPOSTX/ProbTrackX tractography algorithm implemented in FMRIB Diffusion was used to reconstruct tracts of interest with a two-fibre model, 5000 streamlines per voxel, 0.5 mm step length and a curvature threshold of 0.2 (Nomura et al., 2010). The bilateral DLPFC was set as the seed, the corpus callosum (also extracted from AAL templates) as the exclusion mask and the bilateral thalamus as the termination mask. The streamlines originating from the unilateral DLPFC to the ipsilateral thalamus were summated as the connectivity from the seed to target region. Then, the left and right DLPFC-thalamus fibers were determined, respectively. Subsequently, the GLM was used to compare fiber numbers among the normal ECF, impaired ECF and HC groups ($p < 0.05$). The associations of fiber number (FN) and WCST scores were also assessed across patients though partial correlation analysis considering age, sex, and education levels as covariates ($p < 0.05$). SPSS v16 (SPSS, USA) was used for statistical analyses.

2.4. FMRI data preprocessing

Rs-fMRI images underwent a preliminary assessment with Data Processing & Analysis for (Resting-State) Brain Imaging (DPABI) (http://www.rfmri.org/dpabi) (Yan et al., 2016). The initial 10 volumes of each functional time series of each subject were excluded for the stabilization of the participant, with signals reaching equilibrium. Therefore, 170 volumes were submitted to slice timing for correcting slice differences, followed by realignment to the initial volume for head motion correction, using the Friston-24 model; subjects with maximal displacement, maximal rotation and mean framewise displacement (FD) above 2 mm, 2.0°, and 0.3 were not included in the analysis (Yan et al., 2013). Mean FD was considered a covariate for further subgroup analysis to minimize the effects of possible head movement. Friston 24 head motion parameters, mean signal of lateral ventricles, and mean signal of the deep cerebral white matter were submitted to regression. Bandpass filtration (0.01–0.08 Hz) of time series was performed to cut out low frequency drifts and signal variations. Then, data normalization was based on the standard Montreal Neurological Institute (MNI) echo planar imaging (EPI) template with 3 mm isotropic voxels. Next, fMRI data underwent smoothing (6 mm full width at half maximum). It is known that global signal might be tightly associated with underlying neural activity instead of introducing artifacts to connectivity in the resting state (Scholvinck et al., 2010; Chai et al., 2012), In addition, Yang et al. found global signal could help reveal the mechanism of schizophrenia (Yang et al., 2014). Therefore, global signal regression was not selected for data analysis.

2.5. Resting state functional connectivity of the DLPFC-thalamus pathway

Extraction of regional rs-fMRI time series of seeds of the DLPFC-thalamus pathway was performed through calculation of voxel average within regions at individual time points during

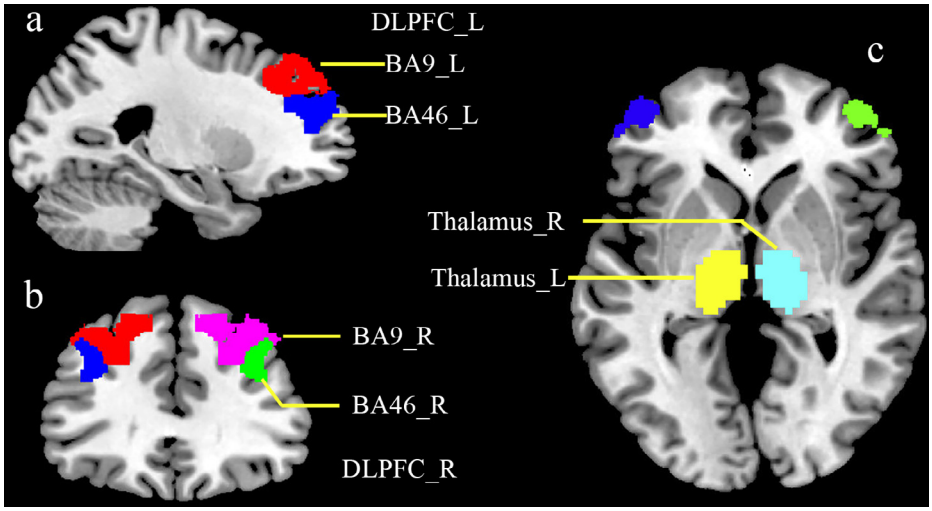

Fig. 2. Seeds of DLPFC-thalamus pathway. (a) sagittal image show the left BA9 and BA46; (b) coronal image show the bilateral BA9 and BA46; (c) transverse image show the bilateral thalamus. BA, brodmann.

preprocessing. FC was assessed by DPABI to generate correlation maps for all voxels with positive or negative correlations with the seed's time series. The resulting r-value maps underwent Fisher's z transformation for approximating Gaussian distribution. One sample t-test was performed on the FC of DLPFC-thalamus pathway in healthy control and patient groups, respectively. Then, the GLM with age, sex and education levels as covariates was used to analyze DLPFC-thalamus FC differences among the normal ECF, impaired ECF and HC groups. Bonferroni correction was employed in multiple comparisons ($p < 0.05$, corrected). Post-hoc analysis was employed to determine FC differences in group pairs ($p < 0.05$, Bonferroni correction). Pearson correlation analysis of FC and various WCST parameters, respectively, was performed taking age, sex and education as covariates ($p < 0.05$). SPSS v16 (SPSS, USA) was used statistical analyses.

3. Results

3.1. Rs-FC alterations of the DLPFC-thalamus pathway

In inter-group FC comparison of the DLPFC-thalamus pathway, significantly different FC was observed only at the left side of the DLPFC-thalamus pathway (between left DLPFC and left thalamus) (Bonferroni corrected $p < 0.05$) among the three groups. The impaired ECF group showed significantly increased FC compared with the normal ECF and HC groups (Bonferroni corrected, $p < 0.05$). FC levels were similar in the latter two groups ($p = 1.000$) (Fig. 3). Furthermore, no significant differences in FC were found for other seed pairs in the DLPFC-thalamus pathway.

3.2. Absolute number of PFC-thalamus connections

The DLPFC-thalamic FN is reflected by the sum of streamlines origination from DLPFC and reaching the ipsilateral thalamus. Representative probabilistic tracking fiber bundles for each group were showed in Fig. 4. The absolute number of fibers of the left side of the DLPFC-thalamus pathway (between left DLPFC and left thalamus) was significantly increased in the impaired ECF group ($3.3225 \times 10^6 \pm 1.0636 \times 10^5$) compared with the normal ECF ($3.231 \times 10^6 \pm 1.9262 \times 10^5$) and HC ($3.2289 \times 10^6 \pm 1.01363 \times 10^5$) groups ($p < 0.05$), with the latter two groups showing similar values ($p = 1.000$) (Fig. 4). In addition, FNs in the right DLPFC-thalamus pathway were similar in all three groups ($p = 1.000$).

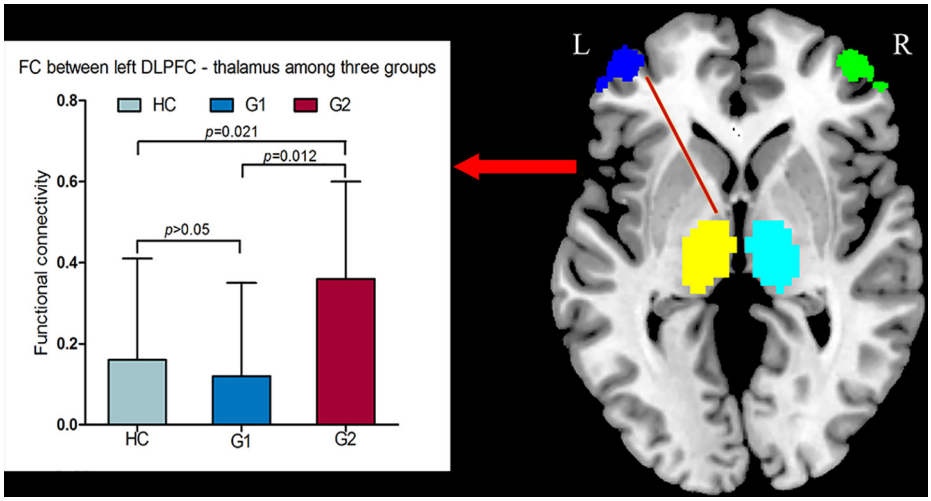

Fig. 3. FC comparison of left DLPFC-thalamus pathway among three groups. G2 exhibited significantly increased FC compared with G1 and HC ($p < 0.05$, Bonferroni corrected); G1 showed no significant difference of FC compared with HC. The red line indicates increased FC. FC, functional connectivity; G2, impaired ECF group; G1, normal ECF group; HC, healthy control group.

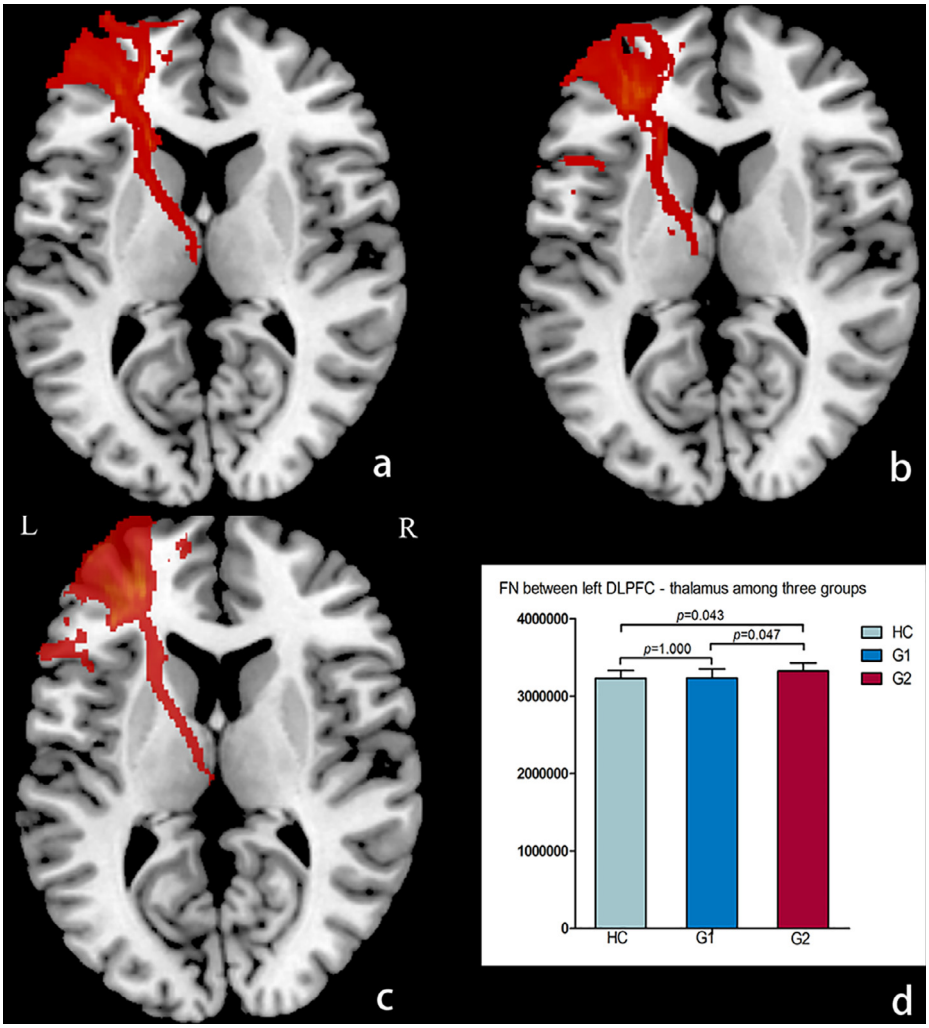

Fig. 4. Representative probabilistic tracking fiber bundles of DLPFC-thalamus pathway of impaired ECF group (a), normal ECF group (b) and healthy controls (c), respectively. (d), FN comparison of left DLPFC-thalamus pathway among three groups. G2 exhibited significantly increased FN compared with G1 and HC ($p < 0.05$, Bonferroni corrected); G1 showed no significant difference of FC compared with HC. FN, fiber number; G2, impaired ECF group; G1, normal ECF group; HC, healthy control group.

3.3. Associations of FC and FN alteration with WCST

In correlation analysis of the bilateral DLPFC and thalamic connectivity with WCST performance, respectively, FC and FN were not associated with WCST parameters in the normal ECF, impaired ECF and HC groups in the present study (all $p > 0.05$).

4. Discussion

The current study revealed increased structural and functional connectivity of the DLPFC-thalamus pathway in unilateral TLE with ECF impairment. Unlike our previous study, we further evaluated structural and functional connectivity alterations using hypothesis-based approach in individuals with unilateral intractable TLE showing ECF impairment. The present findings were consistent with the notion that the thalamus shares reciprocal connectivity with PFC (Hetu et al., 2013; Schoeler et al., 2014), and corroborated a previous report demonstrating that the DLPFC-thalamus pathway is altered in epilepsy with ECF deficits (Borlot et al., 2014). In addition, we found that patients with impaired ECF showed the same pattern of increased structure and functional connection ipsilaterally to epileptogenic foci, also in agreement with previously reported findings that thalamic functional connection changes are sensitive and specific to seizure onset laterality in TLE (Barron et al., 2015). This counterintuitive finding suggests a dysfunctional remodeling of the DLPFC-thalamus pathway in left TLE, and enhanced functional and structural connectivity with a loss in cognitive function.

Compared with other types of epilepsy, TLE with HS results in even worse WCST performance (Giovagnoli, 2001), because epileptogenic foci are more common at the left side than the right one (Horel, 1994). These reports indicated that patients with left TLE are more likely to develop ECF disorders. A possible explanation is that working memory, which is supported by the hippocampus, is involved in the WCST test (Winston et al., 2013). However, other studies refuted this 'hippocampal contribution' hypothesis (Hermann and Seidenberg, 1995a, Martin et al., 2000). Another reason why TLE patients with HS develop ECF impairment is that epileptiform discharges stemming from the diseased temporal lobe propagate to prefrontal lobes, further disturbing cognitive function sub-served by the latter (Spellman et al., 2015; Reyes et al., 2018).

The VBM study confirmed that frontal lobe atrophy has a direct relationship with ECF impairment in unilateral TLE with HS. In addition, TLE patients with HS do not show declined WCST performance after surgical resection of the hippocampus, which also supported the above hypothesis (Tisser et al., 2007).

ECF involves a broad network of cortical and subcortical regions, such as the dorsolateral and medial prefrontal cortices, thalamus, and basal ganglia (Borlot et al., 2014; Di Rienzo et al., 2014; Voets et al., 2015). There is a direct, interactive communication between the thalamus and the prefrontal lobe (Schoeler et al., 2014). It is conceivable that disruption of the pathway between bilateral thalamus and the prefrontal lobe might cause ECF impairment. However, the interaction between PFC and the thalamus in cognitive processing in unilateral TLE remains largely undefined.

The thalamus is an important hub in seizure initiation, propagation, and modulation in experimental and clinical epilepsy (Hetu et al., 2013; Yoon et al., 2013). Previous studies reported the thalamus is frequently involved in the limbic seizure circuit, especially closely interacting with frontal lobes (Hermann et al., 1995b; Helmstaedter et al., 2003). Neuroimaging showed the thalamic volume is prone to decrease in mesial TLE compared with other types of epilepsy (Helmstaedter et al., 2003), and such alterations were pathologically identified as a loss of neurons of the thalamus attacked by epileptiform discharges originating from the temporal lobe (Yoon et al., 2013).

Although connections in the limbic circuit are altered by seizure propagating in TLE, Bonelli and Cummings (2007) found paradoxical structural connectivity increase in limbic structures through the DTI study, likely due to the potential reorganization of the limbic system. Induction of thalamic connectivity during seizures owes to coupling of thalamus cell loss and synaptic alterations (Bertram et al., 2001). These findings indicate that the thalamus is a vulnerable hub in seizure activities in TLE, and may be closely associated with structure and function remodeling.

PFC shares complex neural connections with the thalamus, caudate nucleus, globus pallidus, amygdala and hippocampus, which organize an important circuit for maintaining cognitive functions (Royall et al., 2002). Meanwhile, cognitive function is affected by seizure attacks involving connections with PFC in patients with TLE (Bell et al., 2011). A previous VBM study suggested PFC is an important structure as an occult regulator of epileptogenesis, and decreased PFC volume reflects the outcome of seizure attack (Doucet et al., 2015). Further study revealed disrupted white matter link with frontal lobe is limited within the ictal hemisphere in TLE (Lin et al., 2008).

Single photon emission computed tomography (SPECT) assessment found that the frontal lobe shows abnormal perfusion during the seizure interictal period (Takaya et al., 2006). Meanwhile, fMRI also revealed abnormal FC between the hippocampal and anterior prefrontal lobe in left TLE patients (Kemmotsu et al., 2013). Therefore, both structural and functional MRI studies suggested that the PFC is another important hub involved in TLE with cognitive dysfunction.

As a core structure of the PFC in performing ECF (Royall et al., 2002), DLPFC was revealed predominantly, accounting for ECF impairment in unilateral TLE, as assessed by a voxel-based morphometry (VBM) study (Di Rienzo et al., 2014), which further pinpointed the location of frontal abnormalities to the sub-region of DLPFC, consistent with findings by previous animal and human studies that DLPFC is closely associated with ECF performance (Weinstein et al., 2012; Orellana and Slachevsky, 2013). So, the current study mainly focused on DLPFC.

The thalamus and frontal lobes are included in cortico-subcortical circuits, which regulate ECF (Bonelli and Cummings, 2007; Thakkar et al., 2014). MRI assessment further demonstrated structural and functional connectivities linking the thalamus and DLPFC in humans, e.g. fiber connections between the thalamus and PFC could be reconstructed by the probabilistic tracking method (Nomura et al., 2010; Borlot et al., 2014), and functional connections between these two structures were also demonstrated by rs-fMRI (Ji et al., 2013; Crittenden and Mitchell, 2015).

ECF impairment may represent specific disease-related processes involving the DLPFC-thalamus pathway. No significant associations of abnormal fiber count and FC with WCST score were found. These findings indicates that enhanced DLPFC-thalamus wiring could reflect the remodeling of the disrupted pathway altered by seizure spread, which may fail to compensate for ECF damage. This inverse relationship was consistent with previous structural and functional network reports assessing in TLE (Dalrymple-Alford et al., 2010; Voets et al., 2014).

5. Limitations

This study had two limitations. First, only left-hemisphere TLE cases were assessed, and inclusion of right-hemisphere TLE cases would yield more comprehensive conclusions. Secondly, probabilistic tractography with FSL is limited in signal-to-noise ratio and white matter boundary.

6. Conclusion

The current findings suggest that the DLPFC-thalamus pathway is closely associated with ECF impairment in unilateral TLE patients, and increased connectivity between DLPFC and the thalamus is localized ipsilaterally to the epileptogenic focus. The pathological pattern of the DLPFC-thalamus pathway might emulate structural and functional remodeling along the seizure propagation pathway, but could not compensate for ECF performance. The DLPFC-thalamus pathway may be an important structure for exploring the mechanism of such disorder.

Competing financial interests

The authors declare no competing financial interests.

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