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Effect of lateralized temporal lobe epilepsy on the default mode network

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Abstract

The default mode network (DMN) is composed of cerebral regions involved in conscious, resting state cognition. The hippocampus is an essential component of this network. Here, the DMN in TLE is compared to control subjects to better understand its involvement in TLE. We performed resting state connectivity analysis using regions of interest (ROIs) in the retrosplenium/precuneus (Rsp/PCUN) and the ventro-medial pre-frontal cortex (vmPFC) in 36 subjects (11 with right TLE, 12 with left TLE, 13 controls) to delineate the posterior and anterior DMN regions respectively. We found reduced connectivity of the posterior to the anterior DMN in patients with both right and left TLE. However, the posterior and anterior networks were found to be individually preserved. Lateralization of TLE affects the DMN with left TLE demonstrating more extensive networks. These DMN changes may be relevant to altered cognition and memory in TLE and may be relevant to right vs. left TLE differences in cognitive involvement.

Keywords

Temporal Lobe Epilepsy (TLE); Default mode network (DMN); fMRI; Functional connectivity; Epilepsy psychopathology; Epileptic networks

1. Introduction

The default mode network (DMN) comprises a set of brain regions that has been shown to be active when awake individuals are undisturbed and engaged in spontaneous thoughts [1–3]. It was initially identified in regional cerebral blood flow studies using 133-Xe and 15-O PET studies [4,5]. Subsequently, resting state fMRI has been used extensively to elucidate properties of this network [1]. The DMN is composed of the ventro-medial pre-frontal cortex (vmPFC), posterior cingulate cortex (PCC), retrosplenial cortex (Rsp) including precuneus (PCUN), the inferior parietal lobules (IPL), lateral temporal cortices, and the

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hippocampal formations [3]. The DMN has been implied as a substrate for the conscious state and has been recognized to be altered in conditions affecting consciousness (e.g., absence seizures), memory (e.g. Alzheimer's disease), and social cognition (e.g., autism and schizophrenia) [6–10].

Previous studies have indicated involvement of the DMN in temporal lobe epilepsy (TLE). Ictal SPECT in TLE has shown reductions in blood flow to the DMN in seizures with reduced consciousness [11,12]. Simultaneous EEG–fMRI has revealed decreased signal within the DMN during interictal epileptiform discharges in TLE [13,14], idiopathic generalized epilepsy [15,16], and secondarily generalized epilepsy [16]. Such changes do not occur with extra-temporal focal epilepsy [13]. Overall, these results indicate the possibility of an important role of the DMN in the interictal electrographic and the ictal behavioral manifestation of seizures with loss of awareness.

The temporal lobe is intricately connected to the DMN, and secondary involvement of the DMN may be a mechanism mediating the effects of TLE on consciousness and cognition. The hippocampus has well-defined structural and functional connectivity to the posterior regions of the DMN [3,17]. Involvement of the temporal lobe in TLE is likely to affect the DMN as has been proven in other conditions affecting the temporal lobe/limbic system such as Alzheimer's disease [6,10] and schizophrenia [9]. Previous studies have primarily looked at the involvement of the DMN in TLE during seizures or during IEDs. Resting state fMRI connectivity of the DMN in lateralized TLE has been described in one publication, and this investigation used a different analytical approach [18].

In the present study, we used ROI-based functional connectivity MRI (fcMRI) to further evaluate the DMN in TLE during the basal state without respect to seizures or IEDs to better understand the impact of TLE on the DMN. According to the hub and spoke model of the default network, there are multiple sub-systems within the DMN, the predominant ones being the posterior midline (Rsp/PCUN) and pre-frontal regions (vmPFC). Hence, we separately examine the connectivity patterns of these two main hubs of the DMN — the posterior (Rsp/PCUN) and anterior (vmPFC) regions to examine the effects of TLE on their interconnectivity and changes in their associated sub-networks.

2. Methods

2.1. Subjects

The study population of 36 subjects included 11 with right TLE, 12 with left TLE, and 13 controls (Table 1). Written informed consent was obtained prior to scanning from all subjects in accordance with the guidelines of the University of California, Los Angeles (UCLA) Institutional Review Board that approved the study and in compliance with the 1964 Declaration of Helsinki. Control subjects were recruited locally at UCLA. Each had a normal structural MRI, and none had a history of neurologic illness or were taking a neurologic medication. Epilepsy subjects were patients of the UCLA Seizure Disorder Center who had undergone comprehensive diagnostic testing and were found to be candidates for anterior temporal lobe resective epilepsy surgery. The diagnostic evaluation included video-EEG monitoring, high-resolution MRI, FDG-PET scanning, and

neuropsychological testing (Table 1). Post-operative seizure freedom was assessed at the initial follow-up visit after surgery. Patients remained on their regular medications during the fMRI. None of the patients had a seizure in the 24 h preceding the imaging. Participants were instructed to relax with eyes closed during imaging. No auditory stimulus was present except for the acoustic noise from imaging. None of the patients had seizures during the study as confirmed by the simultaneous EEG obtained during fMRI as part of a related study. The EEG results were not included in the data analysis other than to exclude seizures. The EEGs recorded during the fMRI scan had very rare interictal epileptiform discharges, and there was no difference in discharge number between the patient groups. Details of the simultaneous EEG methods are described in Stern et al. [19].

2.2. Imaging

Imaging was performed with a 3 T MRI system (Siemens Trio, Erlangen, Germany). Functional imaging was performed with the following parameters: TR 2000 ms, TE 30 ms, FOV 210 mm, matrix 64×64, slice thickness 4 mm, 34 slices. High-resolution structural images were obtained during the same imaging study with the parameters: TR 20 ms, TE 3 ms, FOV 256 mm, matrix 256×256, slice thickness 1 mm, 160 slices. The images were acquired in the axial plane using a spoiled gradient recalled (SPGR) sequence for the anatomical images and an echo planar imaging (EPI) sequence for the functional images. Each imaging session included multiple simultaneous EEG and fMRI recordings, each lasting 5 to 15 min and combining to include 30 to 45 min in total. From this, for each subject, two consecutive runs of 10 min each (total 20 min) were used for fMRI connectivity analysis.

2.3. Pre-processing

Pre-processing of the fMRI data was performed using FSL (fMRIB Software Library) version 4.1.6 (Oxford, UK, www.fmrib.ox.ac.uk/fsl) [20,21], which included head movement artifact removal [22], non-brain tissue elimination [23], regression using 6 motion parameters and their derivatives, high-pass filtering (100 s), spatial smoothing at 5 mm full-width half-maximum, and mean-based intensity normalization as described previously for resting state fMRI analyses [24,25]. The normalized residuals from this analysis were then used in the seed based analysis.

2.4. Statistical methods

The residuals from the above analysis were then used in the ROI-based correlation analysis. ROIs with a diameter of 6 mm were defined in the standard MNI space centered by coordinates corresponding to the Rsp/PCUN region ($x=0$, $y=-51$, $z=32$) and the ventro-medial pre-frontal cortex (vmPFC; $x=3$, $y=60$, $z=-1$) using techniques that have been previously described [1,25] (Fig. 1). We used Rsp/ PCUN and the vmPFC as the ROIs as they are two of the major hubs of the DMN [3].

Subsequently, these ROIs were transformed from the standard MNI space to each subject's individual brain space. Partial correlations between voxels within the ROI and all other voxels in the brain were calculated separately for each run of each subject. To combine these values across runs, we applied a Fisher's Z transform (FZT) to the correlation maps

calculated in the previous step. The residuals from the first nuisance analysis were conditioned for the FZT by removing the mean and dividing by the standard deviation, thus centering the distribution around zero and setting the standard deviation to 1. Ordinary least squares (OLS) simple mixed effect analysis was used to combine data over runs within each subject and subsequently, to combine estimates between subjects in a group model. The data were transformed from Fisher's z-scores back to correlation coefficients to help with interpretation of the resulting parametric maps.

The group analysis was performed voxel-wise, using a one-way ANOVA with three levels corresponding to the three groups (right TLE, left TLE, and control subjects). Specific contrasts performed included [1] right TLE greater than controls; [2] left TLE greater than controls; [3] right TLE greater than left TLE; [4] left TLE greater than right TLE; [5] control greater than right TLE; [6] control greater than left TLE; [7] TLE (combined right and left) greater than control; and [7] control greater than TLE (combined right and left). Gaussian field theory was used to threshold Z statistic images, using a cluster forming threshold of $Z > 2.0$ and a corrected cluster significant threshold of $p = 0.05$ [26].

Between group differences in the demographic- and epilepsy-related measures were analyzed using IBM SPSS Statistics, Release Version 19.0.0 (SPSS, Inc., 2010). The age and gender were compared between the three groups using the Kruskal–Wallis and Chi-squared tests respectively. Among patients, the age at epilepsy onset, epilepsy duration, and seizure frequency were compared using the Mann–Whitney *U* test.

3. Results

The clinical characteristics of the participants are given in Table 1. Comparison of demographic- and epilepsy-related characteristics between the subjects is shown in Table 2.

The presumed underlying etiology of TLE based on pre-surgical MRI was heterogeneous (Table 1) with mesial temporal sclerosis being the most common etiology; MRI evidence suggested that seven out of twelve patients with left TLE and four out of eleven patients with right TLE had mesial temporal sclerosis (Table 1).

3.1. Posterior (Rsp/PCUN) ROI

A network correlated to the posterior ROI was identified in all three groups (Figs. 2A, B, C, Table 3). Compared with control subjects, patients with TLE had bilaterally reduced connectivity of the seed area (Rsp/PCUN) to the anterior (medial frontal) components of the DMN (Figs. 2F, G, K, Table 3). In addition, patients with right TLE had reduced connectivity to the right antero-medial temporal lobe (Fig. 2F) and the posterior DMN (Figs. 2F, I, Table 3). Subjects with left TLE had bilaterally increased connectivity to the opercular areas (Figs. 2E, I, Table 3). Other comparisons performed (2-D, 2-H, 2-J) did not yield significant results.

3.2. Anterior (vmPFC) ROI

An anterior network correlated to the anterior ROI was identified in all three groups (Figs. 3A, B, C, Table 4). Compared with control subjects, patients with left TLE had reduced

connectivity of the seed area (vmPFC) to bilateral posterior (hippocampus, parahippocampal, fusiform, lingual, cingulate) networks (Fig. 3G, Table 4). A similar finding was also seen in controls compared with TLE (Fig. 3K). Left TLE seemed to have the major effect in these comparisons as evident by lack of significant difference between control subjects and those with right TLE (Figs. 3D, F). Patients with left TLE had a more extensive bilateral anterior (fronto-centro-parietal) network compared with control subjects and those with right TLE (Figs. 3E, I). A similar finding was also seen in patients with TLE compared to controls (Fig. 3J). Other comparisons performed (Figs. 3D, F, H) did not yield significant results.

4. Discussion

Using ROI-based connectivity of the posterior and anterior parts of the DMN, we identified a difference in the DMN between TLE and controls and also between right TLE and left TLE. Regardless of lateralization, in patients with TLE showed reduced connectivity between the posterior DMN to the anterior portions of the DMN. Patients with left TLE showed increased connectivity of the posterior DMN to bilateral opercular areas and the anterior DMN to bilateral fronto-centro-parietal areas. In addition, patients with right TLE had reduced connectivity of the posterior DMN to the adjacent areas as well as the ipsilateral (right) antero-medial temporal region (Fig. 2).

4.1. Functional connectivity studies of the DMN in TLE

Resting state fMRI connectivity of the DMN in lateralized TLE has been described in one publication, and this investigation used a different analytical approach [18]. Consistent with our findings, this study, which used independent component analysis (ICA) to determine the connectivity of the subcomponents of the DMN in patients with TLE, found reduced connectivity in the dorsal medial pre-frontal cortex in both patients with right TLE and those with left TLE compared with controls [27]. However, our vmPFC ROI-based analysis shows that an anterior network not only exists in TLE, but also is more extensive in patients with left TLE than in control subjects. We propose that the appearance of a reduced anterior sub-network with the posterior ROI connectivity analysis is likely secondary to disconnection of the anterior from the posterior DMN. Such a disconnection between the posterior and anterior DMN has previously been shown in idiopathic generalized epilepsy [28], but not in TLE. We were also able to replicate the involvement of the mesial temporal component of the DMN in MTLE similar to the prior study [18]. In addition, we identified a previously undescribed increase in connectivity of the posterior DMN to the opercular areas and the anterior DMN to the fronto-centro-parietal areas in left TLE.

A discordant change in the connectivity of the posterior and anterior DMN has been previously noted in other conditions primarily affecting the temporal lobe and limbic system such as Alzheimer's disease [10] and schizophrenia [9]. In normal aging, the anterior DMN has been noted to have reduced integrity or variably increased/ decreased connectivity [10,29]. Reduced connectivity of the anterior DMN has also been noted in bipolar disease [30,31]. Functionally, the posterior DMN is thought to be involved in simultaneous monitoring of endogenous and exogenous states [32], while the anterior DMN is concerned with introspection and social cognition [33,34].

A recent study investigating the connectivity patterns of ipsi-lesional and contra-lesional amygdala and hippocampus in lateralized TLE determined that there was markedly reduced connectivity of both hippocampi to the ventro-mesial pre-frontal region (anterior DMN), and to a lesser extent, with the posterior DMN [35]. As both the hippocampal formation and the anterior DMN are strongly linked to the posterior DMN, but not to each other [3], a disconnection between the posterior and anterior DMN as we demonstrate could lead to reduced connectivity between the hippocampus and the anterior DMN. Also consistent with their results, we showed reduced connectivity of the posterior and anterior DMN to the ipsilateral hippocampus in right and left TLE respectively (Figs. 2F and 3G).

A previous study which performed ROI-based analysis during a memory task concluded that the connectivity of the PCUN was affected more in left TLE compared with right TLE [36], which is contrary to our finding of greater reduction of connectivity with right TLE. However, this study examined connectivity not in the resting state, but during a task paradigm which is known to affect connectivity patterns [37]. Reduced connectivity between the mesial temporal lobes and the PCC/ PCUN has been shown in patients with bilateral TLE [38]. In unilateral TLE, we were able to show such an effect in right, but not in left TLE. A recent study on seven patients with TLE showed reduction in the extent of multiple resting state networks including the posterior and anterior DMN consistent with our findings. However, the study had only five patients with left and two with right TLE, and a sub-analysis between right and left TLE was not reported [39].

4.2. Differential involvement of cerebral networks in right TLE and left TLE

We found reduced posterior DMN connectivity in patients with right TLE and increased connectivity of the posterior and anterior DMN in patients with left TLE, suggesting a general reduction in connectivity in right TLE and increased connectivity in left TLE. This lateralized connectivity asymmetry is consistent with a recent study of resting state fMRI showing increased influence of the contralateral hippocampus on the ipsi-lesional hippocampus in right TLE, but not in left TLE [14]. Another resting state fMRI study of TLE showed pronounced ipsi-lesional hippocampal connectivity impairment in left TLE and less marked impairment in right TLE compared to controls [40]. This suggests that the increased connectivity in left TLE that we observed could represent extra-hippocampal increase in connectivity to compensate for the decreased hippocampal connectivity. Increased connectivity of left TLE compared with right TLE is also demonstrated by task-based functional MRI studies of language and memory tasks in TLE, which generally reveal a redistribution of function in left TLE and bilateral impairment in right TLE [41–44]. The differences between DMN connectivity in left and right TLE could underlie some of the cognitive change differences noted between the two subtypes of TLE.

It is also plausible that innate side-to-side cerebral asymmetry and dominance pattern could contribute to the observed difference in connectivity between right TLE and left TLE. Tractography in healthy subjects has revealed more prominent structural connectivity in the left, compared with the right hemisphere [45]. Healthy subjects also have increased connectivity within the left, as compared with the right basal temporal lobe [46]. We postulate that the greater extent of left hemispheric connectivity in the healthy brain

evidenced by these studies may confer additional functional integrity that is protective in left-sided disease against the proven network-disruptive effects of TLE [46]. In other words, DMN disruption may be more likely in right TLE compared to left TLE on account of the greater normal left hemispheric connectivity at baseline.

4.3. Limitations

The two epilepsy subject groups were homogeneous for lateralization based on a comprehensive, epilepsy surgery evaluation, but the individual subjects differed in the underlying etiologies (Table 1). It is plausible that distinct TLE subtypes may have different effects on brain networks. Since the functional abnormality, as clinically manifested, was homogeneous within each epilepsy group, a grouping as right and left TLE is reasonable for an initial DMN investigation of TLE. Another potential confound is the variation in the antiepileptic drugs (AEDs) used in our patient groups. It is possible that AEDs affect functional connectivity given that they primarily act on the brain. The large number of available AEDs and the complexity of therapeutic regimens will make it difficult to investigate the connectivity effects of individual AEDs. Handedness is another possible confound that may influence our results [47]. Although three patients with left TLE were left-handed, an analysis that excluded them did not result in different correlation patterns, and they were included in the final analyses.

4.4. Conclusions

Our ROI-based functional connectivity study of the DMN identified abnormal reduction in connectivity between the anterior and posterior portions of the DMN in both patients with right and left TLE. Cognitive deficits and behavioral/mood changes described in TLE could be related to this as a similar disconnection has been seen in conditions affecting memory and behavior such as Alzheimer's disease, schizophrenia, and bipolar disease. The study also identified differences between right and left TLE with enhanced PCUN/Rsp to opercular connectivity and enhanced vmPFC to fronto-centro-parietal connectivity in left TLE and reduced PCUN/Rsp to right antero-medial temporal connectivity in right TLE. This could represent compensatory responses to increased disruption of normal networks in left compared to right TLE. Our findings add to the understanding of the interictal network abnormality in TLE, which is relevant to its underlying pathophysiology independent of seizure and IED occurrence.

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Fig. 1.
Locations of seeds used for correlation analysis Rsp/PCUN (MNI coordinates 0, -51, 32)
and vmPFC (MNI coordinates 3, 60, -1).

Fig. 2.

Comparison of posterior seed correlation between groups (see Table 2/results for details) at $z > 2.0$, $p = 0.05$. Other comparisons did not yield significant differences. Brain orientation is radiological (image right side is subject's left side). Color bars represent z-scores. C=control; R=right TLE; L=left TLE.

Fig. 3.

Comparison of anterior seed correlation between groups (see Table 3/results for details) at $z > 2.0$, $p = 0.05$. Other comparisons did not yield significant differences. Brain orientation is radiological (image right side is subject's left side). Color bars represent z-scores. C=control; R=right TLE; L=left TLE.

Table 1

Clinical characteristics of participants.

Age	Sex	Handedness	Sz onset age (yr)	Sz duration (yrs)	Sz freq (/month)	AEDs	MRI	Pathology	Sz free post-surgery (last follow-up)	Time since surgery (months)	Neuropsychology memory dysfunction
<i>Right TLE</i>											
34	M	R	15	19	3	LTG	R MTS	Gliosis	Yes	27	NV
34	F	R	14	20	60	LEV, LTG	R temporal hyperintensity	Gliosis	No	20	NV
43	M	R	41	2	1	LEV, LTG	Normal	No surgery	Yes	No surgery	Not done
35	F	R	12	23	16	LEV, TPM, LTG	R MTS	Insuff. sample	No	7	NV
40	M	R	20	20	3	VPA, LCM	R amygdala hypertrophy	Insuff. sample	Yes	3	NV
39	M	R	8	31	2	LTG, LEV	R MTS	Gliosis	Yes	1.5	Normal
52	M	R	47	5	2	LEV	R temporal CD	Mild CD	No	17	NV>V
53	F	R	45	8	3	OXC	Normal	Mild cortical disorganization	Yes	18	NV
45	F	R	36	9	2	VPA, LCM	Hipp. malformation	Gliosis	Yes	7	Not done
20	M	R	1	19	2	OXC, LCM	Bilateral hipp. atrophy	Gliosis	Yes	3	NV
47	M	R	10	37	2	VPA, LEV	R MTS	MTS	Yes	1	NV
<i>Left TLE</i>											
40	F	R	38	2	3	OXC	Hipp. signal abnormality/atrophy	CD	Yes	23	Inconclusive
40	M	R	20	20	1	LTG, OXC	Normal	Normal	LTF	18	Normal
40	M	R	4	36	3	LEV, LTG	L MTS	MTS+CD	Yes	18	V>NV
35	F	R	6	29	2	CBZ, LEV, LTG	L MTS	Gliosis	Yes	4	B (L>R) TL dysfunction
36	F	R	3	33	10	PHT, PB, LEV	L MTS	No surgery	No surgery	No surgery	Normal
23	F	R	17	6	7	PHT	L hipp. hyperintensity	CD	Yes	23	V
20	F	R	12	8	7	VPA, PGB	Normal	CD	Yes	17	Normal
27	F	L	9	18	1	PHT, LTG, LEV	L MTS	CD	Yes	15	V
46	F	L	1	45	5	LTG, LCM	L MTS	CD	Yes	8	NV+V
45	M	L	40	5	2	LEV	L MTS	Normal	Yes	5	NV+V
30	M	R	14	16	5	LEV, CBZ, LCM	L anterior temporal signal abnormality	CD	Yes	2	V
52	M	R	46	6	60	PHT, LTG	L MTS+anterior temporal CD	HS	Yes	1	V

CBZ — carbamazepine, CD — cortical dysplasia, Hipp — hippocampal, L — left, LEV — levetiracetam, LTG — lamotrigine, MTS — mesial temporal sclerosis, NV — non-verbal, OXC —oxcarbazepine, PB — phenobarbital, PGB — pregabalin, PHT — phenytoin, R — right, SF — seizure free (without surgery), Sz — seizure, LTF — lost to follow-up (this is a patient who did not return for follow-up visits after surgery), VPA — valproate, V — verbal.

Table 2

Analysis of demographic- and seizure-related characteristics between groups.

	Right TLE (n=11)	Left TLE (n=12)	Control subjects (n=13)	Significant difference between groups (p value)
Gender (male/female)	7/4	5/7	9/4	0.34 (NS)
Handedness (right/left)	11/0	9/3	13/0	
Age (mean±SD yrs)	40.2±9.5	36.2±9.7	33.3±10.5	0.14 (NS)
Age at epilepsy onset (mean±SD yrs)	22.6±16.5	17.5±15.5	NA	0.39 (NS)
Epilepsy duration (mean±SD yrs)	17.6±10.8	18.7±14.2	NA	0.88 (NS)
Median seizure frequency	2–3	2–7	NA	0.45 (NS)

NA – not applicable; NS — non-significant.

Table 3

Areas with significant activity in contrasts of DMN PCUN seed ($z > 2.0$, $p < 0.05$).

Anatomic area	Voxels	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)
<i>Control > right TLE</i>				
Bilateral medial frontal cortex (paracingulate)	34,096	-4	54	-13
Bilateral posterior DMN (precuneus and intracalcarine with extension into supracalcarine and lingual cortices)	31,759	-10	-63	12
Right temporal (middle temporal gyrus, temporal pole and hippocampal head)	23,799	19	-21	-20
<i>Control > left TLE</i>				
Bilateral medial frontal cortex (paracingulate with minimal superior frontal gyrus extension)	33,681	-3	44	5
<i>Control > TLE (left+right)</i>				
Bilateral medial frontal cortex (paracingulate, medial frontal, cingulate with extension to superior frontal, frontal pole and right caudate)	58,207	0	46	8
<i>Left TLE > control</i>				
Left peri-opercular cortex (Heschl's gyrus, planum temporale, post-central gyrus, parietal operculum), insula	25,870	-67	-31	27
Right peri-opercular cortex (Heschl's gyrus, planum temporale, post-central gyrus, parietal operculum), insula	12,992	48	-3	8
<i>Left TLE > right TLE</i>				
Bilateral posterior DMN (precuneus, intracalcarine cortex, occipital fusiform gyrus, lingual gyrus and occipital pole)	46,607	22	-97	-4
Left peri-opercular (insula, planum temporale, central opercular cortex, superior temporal gyrus, supramarginal gyrus)	17,208	-31	-25	7
Right peri-opercular (insula, planum temporale, central opercular cortex, superior temporal gyrus)	13,876	41	1	-7

Table 4

Areas with significant activity in contrasts of DMN anterior seed ($z > 2.0$, $p < 0.05$).

Anatomic area	Voxels	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)
<i>Control > left TLE</i>				
Left hippocampus, parahippocampal, fusiform, lingual, and cingulate gyri, right parahippocampal and cingulate gyri, bilateral thalamus	18,689	4.38	-26	-30
<i>Control > TLE (left+right)</i>				
Left parahippocampal gyrus, hippocampus, amygdala, fusiform, cingulate, R parahippocampal, brainstem	12,908	3.67	11	-8
<i>Left TLE > control</i>				
Left frontal pole, inferior frontal gyrus, fronto-centro-parietal operculum, supramarginal gyrus, post/precentral gyri	118,409	4.9	-47	10
Right frontal pole, inferior frontal gyrus, fronto-centro-parietal operculum, supramarginal gyrus, post/precentral gyri	106,681	4.75	58	-13
<i>Left TLE > right TLE</i>				
Left insula, frontal pole, inferior/middle frontal gyri, precentral gyrus	31,062	4.33	-47	10
Right insula, frontal pole, Inferior frontal gyrus, fronto-parietal operculum, precentral gyrus	29,428	4.24	48	-29
<i>TLE (left+right) > control</i>				
Left frontal pole, inferior/middle/superior frontal gyri, insula, centro-parietal operculum, sup temporal, supramarginal, pre- and post-central cortices.	68,997	3.88	-47	10
Right frontal pole, inferior/middle/superior frontal gyri, insula, centro-parietal operculum, sup temporal, supramarginal, pre- and post-central cortices.	67,163	4.07	62	-17
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