Running Head: FUNCTIONAL CONNECTIVITY IN EPILEPSY

Title: Altered functional connectivity in mesial temporal lobe epilepsy

Authors: Hana Burianová[1,2*], Nahla L. Faizo[2*], Marcus Gray[2], Julia Hocking[3], Graham Galloway[2,4], David Reutens[2,5]

[1]Department of Psychology, Swansea University, Swansea, United Kingdom
[2]Centre for Advanced Imaging, University of Queensland, Brisbane, Australia
[3]Institute of Health Biomedical Innovation, Queensland University of Technology, Brisbane, Australia
[4]Translational Research Institute, Brisbane, Australia
[5]Royal Brisbane and Women's Hospital, Brisbane, Australia

Correspondence should be addressed to:
David Reutens
Centre for Advanced Imaging
The University of Queensland
Brisbane, QLD, 4072, AUSTRALIA
d.reutens@uq.edu.au

H. B. & N.L.F. contributed equally to this manuscript.

Acknowledgements: The authors thank the participants for their time and acknowledge the invaluable practical support provided by Dr Lars Marstaller and the imaging staff at the Centre for Advanced Imaging, as well as the technical assistance of the Queensland node of the National Imaging Facility.

Abstract

Growing evidence of altered functional connectivity suggests that mesial temporal lobe epilepsy (mTLE) alters not only hippocampal networks, but also a number of resting state networks. These highly coherent, yet functionally distinct brain circuits interact dynamically with each other in order to mediate consciousness, memory, and attention. However, little is currently known about the modulation of these networks by epileptiform activity, such as interictal spikes and seizures. The objective of the study was to use simultaneous EEG-fMRI to investigate functional connectivity in three resting state networks: default mode network (DMN), salience network (SN), and dorsal attentional network (DAN) in patients with mTLE compared to a healthy cohort, and in relation to the onset of interictal spikes and the period immediately prior to the spikes. Compared to the healthy participants, mTLE patients showed significant alterations in functional connectivity of all three resting state networks, generally characterized by a lack of functional connectivity to prefrontal areas and increased connectivity to subcortical and posterior areas. Critically, prior to the onset of interictal spikes, compared to resting state, mTLE patients showed a lack of functional connectivity to the DMN and decreased synchronization within the SN and DAN, demonstrating alterations in functional coherence that may be responsible for the generation of epileptiform activity. Our findings demonstrate mTLE-related alterations of connectivity during the resting state as well as in relation to the onset of interictal spikes. These functional changes may underlie epilepsy-related cognitive abnormalities, because higher cognitive functions, such as memory or attention, rely heavily on the coordinated activity of all three resting state networks.

Keywords: mesial temporal lobe epilepsy; default-mode network; dorsal attentional network; salience network; functional connectivity

Altered functional connectivity in mesial temporal lobe epilepsy

In mesial temporal lobe epilepsy (mTLE), the most common form of focal epilepsy, a large-scale hippocampal network mediates the generation of interictal spikes and seizures (Faizo *et al.*, 2014; Hufnagel *et al.*, 2000; Janszky *et al.*, 2001). Recent evidence suggests that mTLE also alters activity in a number of resting state networks (RSNs). These highly coherent and functionally distinct brain circuits (Biswal *et al.*, 1995) interact dynamically with each other to mediate sensorimotor and cognitive functions, including consciousness, memory, or attention (Buckner *et al.*, 2008; Clemens *et al.*, 2011; van den Heuvel & Hulfshoff Pol., 2010). Disruptions of RSNs have been linked to cognitive decline (Andrews-Hanna *et al.*, 2014; Sambataro *et al.*, 2010), depression (Sheline *et al.*, 2010), schizophrenia (Manoliu *et al.*, 2014), and Alzheimer's disease (Zhou *et al.*, 2010). Moreover, growing evidence of aberrant resting state connectivity in temporal lobe epilepsy (Liao *et al.*, 2010; Yuan *et al.*, 2013; Zhang *et al.*, 2010) raises the possibility of a role in epilepsy-related cognitive abnormalities, given the heavy reliance of higher cognitive functions, such as memory retrieval or language production, on the coordinated activity of RSNs.

In mTLE, alterations in RSN function have been studied most extensively in the default mode network (DMN), which comprises the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex, and its key structure: the hippocampus (Greicius *et al.*, 2003; Raichle *et al.*, 2001). In mTLE, studies show decreased connectivity between the hippocampus and the other DMN nodes at rest (Pittau *et al.*, 2012; Zhang *et al.*, 2010) and during interictal discharges, as measured by simultaneous EEG-fMRI (Fahoum *et al.*, 2012; Kobayashi *et al.*, 2006; Laufs *et al.*, 2007). Some argue that such alterations in DMN connectivity may underlie epilepsy-related deficits in declarative memory (Braakman *et al.*, 2012; Lin *et al.*, 2012), as the DMN is known to functionally subserve internally-driven cognitive operations, such as self-referential, language, and memory processes (Buckner *et*

al., 2008; Burianová *et al.*, 2010). Importantly, however, this network also plays a critical role in cognitive processes that are engaged during stimulus-directed tasks, as it dynamically interacts with two other large-scale functional networks: the dorsal attentional network (DAN) and the salience network (SN; Chen *et al.*, 2013; Elton & Gao, 2015; Vatansever *et al.*, 2015). As such, it is feasible to suggest that during higher-level cognitive processing, mTLE-related aberrant hippocampal connectivity would be associated with changes in connectivity not only to the rest of the DMN nodes, but also to interconnected networks.

The DAN, comprising the intraparietal sulcus (IPS) and frontal eye fields (FEF), subserves top-down voluntary attention and visual working memory (Andrews-Hanna *et al.*, 2014; Chen *et al.*, 2013; Corbetta & Shulman, 2002; Spreng *et al.*, 2013). Albeit scarce, the available evidence demonstrates significantly decreased functional connectivity of the DAN in participants with mTLE during top-down attentional tasks (Liao *et al.*, 2010; Zhang *et al.*, 2009) and a correlation between poor performance on the tasks and severity of the connectivity alteration (Zheng *et al.*, 2012). The results of these studies suggest that the impairment in DAN connectivity might underlie attentional deficits in mTLE patients (Fleck *et al.*, 2002; Stella & Maciel, 2003); however, attentional dysfunction in mTLE has also been linked to disruptions in salience network connectivity.

The SN, comprising the dorsal anterior cingulate and fronto-insular cortices, mediates the detection of behaviourally salient stimuli, coordination of attentional resources towards such stimuli, and initiation of cognitive control (Fox *et al.*, 2005; Menon & Uddin, 2010; Seeley *et al.*, 2007; Sridharan *et al.*, 2008). It is speculated that atypical connectivity in the SN could result in interruption of salient information processing, impairing salience detection and coordination of behavioural responses (Uddin, 2014). To date, only one study has examined the intrinsic activity of the SN in epilepsy, showing a significant relationship between the SN and conscious awareness in childhood absence epilepsy (Luo *et al.*, 2014).

However, SN connectivity in mTLE patients has not been investigated, despite the fact that the SN dynamically interacts with its interconnected brain networks, contributing to a variety of complex brain functions, including communication, social behaviour, and self-awareness (Craig, 2009; Menon & Uddin, 2010).

In addition, despite accumulating evidence that deficits in higher-order cognitive functions, which frequently accompany mTLE, may be significantly related to disruptions of functional connectivity in large-scale RSNs, little is currently known about the modulation of these networks by epileptiform activity, such as interical spikes and seizures. Although the relation between interictal spikes and seizures is not fully understood (Avoli *et al.*, 2006), evidence suggests that those neural structures that are involved in generating interictal spikes might be reliable estimators of the network or networks that generate seizures (Dinkelacker *et al.*, 2016; Hufnagel *et al.*, 2000; Marsh *et al.*, 2010). Recent EEG-fMRI findings have demonstrated significant alterations that occur immediately *prior to* the appearance of interictal spikes, both in hemodynamic response (Jacobs *et al.*, 2009; Rathakrishnan *et al.*, 2010) and functional connectivity (Faizo *et al.*, 2014). The objective of the study was to use simultaneous EEG-fMRI, which provides highly spatially resolved three-dimensional maps of brain activity (fMRI) associated with interictal electrical discharges (EEG), to investigate functional connectivity in three resting state networks: DMN, SN, and DAN in participants with mTLE compared to a healthy cohort, and, to examine the relationship between changes in connectivity and the onset of interictal spikes. As these three neural networks are central to cognition and their disruption has been linked to a variety of clinical syndromes, such as traumatic brain injury and Alzheimer's disease (Sharp *et al.*, 2014; Zhou *et al.*, 2010), the ultimate goal of the study was the investigate the impact of mTLE on these RSNs.

Methods

Participants.

Fifteen patients with the diagnosis of mTLE (9 females, mean age: 38 years; 6 males, mean age: 42 years; 10 left and 5 right lateralized) and 15 age- and gender-matched healthy controls participated in this study. All patients were recruited from the Royal Brisbane and Women's Hospital Epilepsy Clinic where they underwent comprehensive clinical assessment and the diagnosis of mTLE was based on the following: (i) seizure semiology consistent with mTLE, (ii) interictal spikes confirmed during in-patient video-EEG monitoring performed within the last year, and (iii) MRI scan consistent with a temporal lobe focus (*i.e.*, the patients had no lesion or they had unilateral hippocampal sclerosis). Patient exclusion criteria included absence of interictal spikes during monitoring, recurrent unprovoked seizures, and the presence of metal implants. Patients' clinical details and spike distributions are summarized in **Table 1**. Healthy controls were screened for current and previous brain injury, neurological and psychiatric disorders. All participants gave signed informed consent approved by the Human Research Ethics Committee (HREC) at the Royal Brisbane Women's Hospital (RBWH) and the Medical Resaerch Ethics Committee of the University of Queensland.

[Insert Table 1 here]

Study procedure.

An MRI compatible 64-channel electrode cap, to record EEG from the patients, was positioned on patients' heads according to the international 10:20 system (applicable for all channel densities below 81, which include our 64 channels (Jurcak *et al.*, 2007) and prepared with a conductive non-abrasive gel (chloride 10%). All electrodes, including the ground (AFz) and reference electrodes (FCz), had an impedance below 5 kilo-ohms. One additional electrode recorded an electrocardiogram from the chest, being optimally positioned nearest to

the heart, as the purpose of the ECG was to record (and subsequently remove) physiological activity interfering with the EEG signal. Patients then underwent a 40-minute resting state, simultaneous EEG-fMRI recording in a 3T Magnetom Trio scanner (Siemens, Erlangen, Germany) and were instructed to remain still, awake, and relaxed with their eyes closed. The control participants underwent only resting state fMRI without the EEG recording.

EEG Data Acquisition & Preprocessing.

EEG data were recorded continuously during fMRI acquisition using Brain Vision recorder software version 1.20.0001 (Brainproducts Co., Munich, Germany). EEG preprocessing was conducted off-line using EEGLAB software (Delorme and Makeig, 2004). Gradient and ballistographic artefacts were removed with the Artefact Slice Template Removal (FASTR) algorithm implemented in EEGLAB. Residual artefacts were removed using Independent Component Analysis (ICA), following which a neurologist reviewed the EEG recordings to identify interictal spikes.

fMRI Data Acquisition and Preprocessing.

A twelve-channel head coil was used to acquire the images and head pads were used to minimize head movements during the scan. A high-resolution T1-weighted MP-RAGE sequence was acquired with the following parameters: 192 slices, repetition time (TR) = 1900 ms, echo time (TE) = 2.13 ms, flip angle = 9^{o}, matrix = 192 x 256 x 256, voxel size = 0.9 mm^3. Images sensitised to BOLD contrast were acquired with a single-shot gradient-echo planar image sequence, using the following parameters: 36 slices, TR = 2.5 sec, TE = 30 ms, flip angle = 90^{o}, field of view (FOV) = 210 mm, matrix = 64 x 64, voxel size = 3.3 mm^3. EEG-fMRI data were collected in six runs, each lasting 5:05 minutes.

fMRI preprocessing was conducted using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) running on MATLAB. Functional images were slice-time corrected, realigned, and resliced using a 6-parameter rigid body spatial transformation

(Friston *et al.*, 1995). The structural scan was coregistered to the mean functional image for each participant and normalized to the MNI template. Spatial smoothing was conducted on all normalized images using an 8mm FWHM Gaussian kernel. Head motion did not exceed 1.5 mm in either group of participants. Partial volume loss was countered by (i) an appropriate segmentation procedure and (ii) an optimal FWHM smoothing kernel.

A standard high-pass filter implemented in SPM was used in a routine preprocessing step to remove low-frequency drifts (*e.g.*, scanner drift). We did not use a low-pass filter for two reasons: (1) it is highly controversial, as it can enhance noise instead of suppressing it due to its lack of independence across time, and, critically, (2) the multivariate partial least squares (PLS) analysis, unlike univariate methods (*e.g.*, SPM), does not use generalized linear model, makes no assumptions about the shape of the hemodynamic response function, and is generally unaffected by noise, as signal is normalized to the onset of interest, permutation tests provide robust statistical assessment at the image level, and bootstrap resampling protects against outliers at the voxel level (Krishnan *et al.*, 2011; McIntosh & Lobaugh, 2004; McIntosh *et al.*, 2004).

fMRI Analysis.

We aimed to (i) compare functional connectivity, during rest, in DMN, SN, and DAN between the patients and healthy controls, and (ii) compare functional connectivity in DMN, SN, and DAN between the pre-spike and spike epochs *within* the patient group. For this purpose, we defined three 10-second epochs according to their relation to interictal spike onset: spike (0–10s), pre-spike (-10 to 0 s), and rest (-20 to -10 s, with no previous spikes in the preceding 45s; Faizo *et al.*, 2014). This time window was chosen because the hemodynamic response function returns to baseline 25 seconds after a single burst of neural activity (*i.e.*, the interictal spike). Our study was designed to examine short-term changes in connectivity, and was based on previous findings that pre-spike BOLD signal alterations are

evident up to 9 seconds before interictal spikes (Jacobs *et al.*, 2009; Pittau *et al.*, 2011). On this basis, we selected the interval between 25 seconds after a spike and 10 seconds before the next spike as baseline. This was an event-related analysis and a total of 186 spike, pre-spike, and rest onsets (*i.e.*, the timepoint at the beginning of each epoch) were included in the analysis. In age- and gender-matched controls, the rest onsets were matched to those of the respective patients. Images from patients with right TLE were flipped along the antero-posterior axis, so that in all patients the seizure focus was on the left. To examine the between-groups (analysis 1) and within group (analysis 2) alterations in functional connectivity, activity in selected seed regions was covaried with activity in the rest of the brain during the resting state. Seed regions were selected using MNI coordinates selected from previous studies (Beucke *et al.*, 2014; Buckner *et al.*, 2009; Woodward *et al.*, 2011), which identified the critical nodes of each resting state network: DMN = posterior cingulate gyrus (PCC; -3 -48 30), SN = insula (INS; -38 16 -2), and DAN = intraparietal sulcus (IPS; -23 -70 46). For each seed, the average BOLD signal intensity was extracted and used for connectivity analyses, during rest, in both patients and controls, using the Partial Least Squares (PLS) analysis (McIntosh, Chau, & Protzner, 2004; McIntosh *et al.*, 1996; for a detailed tutorial and review of PLS, see Krishnan *et al.*, 2011).

PLS identifies significant whole-brain activity patterns related to task demands, measures of behavioural or anatomical covariates, group membership, or activity in a given seed region. Activity patterns are assessed across all brain voxels simultaneously, which is in contrast to mass-univariate analyses, which consider each voxel separately. PLS analysis uses singular value decomposition (SVD) of a single matrix, containing all participants' data to find a set of latent variables (LVs), which are mutually orthogonal dimensions that reduce the complexity of the data set. Each LV consists of a singular image of voxel saliences (*i.e.*, a spatiotemporal pattern of brain activity), a singular profile of task saliences (*i.e.*, a set of

weights that indicate how brain activity in the singular image is related to the experimental conditions, functional seeds, or behavioural/anatomical covariates), and a singular value (*i.e.*, the amount of covariance accounted for by the LV). Diverging relationships between covariates and fMRI data are represented in separate LVs, whereas converging relationships are represented in the same LV. The significance of each LV is assessed by a permutation test, which determines the probability that a singular value from 500 random resamplings of the data is larger than the initially obtained value (McIntosh *et al.*, 1996). In addition to the permutation test, a second and independent step is to determine the reliability of the saliences (or weights) for each brain voxel that characterizes a given spatiotemporal pattern identified by the LVs. To do so, the standard error of each voxel's salience on each LV is estimated by 100 bootstrap resampling steps (Efron & Tibshirani, 1985). Peak voxels with a bootstrap ratio (BSR; *i.e.*, salience/standard error) > 3.0 were considered to be reliable, as these approximate $p < 0.001$ (Sampson *et al.*, 1989). Because extraction of the LVs and corresponding brain images is done in a single analytic step, no correction for multiple comparisons is required.

Results

Between Groups Differences in Functional Connectivity

Default mode network

In healthy controls, functional connectivity analysis with PCC as the seed region showed significant connectivity between the typical DMN regions (Damoiseaux *et al.*, 2006; Koshino *et al.*, 2014): PCC, medial prefrontal cortex (PFC), middle temporal gyrus (MTG), parahippocampus, thalamus, precuneus, and bilateral inferior parietal lobule (IPL). In contrast to healthy controls, mTLE patients demonstrated a significantly different connectivity pattern, ipsilateral to the epileptogenic zone and showing a lack of functional connectivity to medial PFC and parahippocampus, decreased connectivity to bilateral IPL

and MTG, and increased connectivity to bilateral thalamus and precuneus ($p < 0.001$; **Fig 1A)**.

Salience network

In healthy controls, functional connectivity analysis with INS as the seed region showed significant connectivity between the typical SN regions (Seeley *et al.*, 2007; Sridharan *et al.*, 2008): bilateral insula, ventral and dorsal PFC, dorsal anterior cingulate cortex (ACC), and cerebellum. In contrast, mTLE patients demonstrated significantly decreased connectivity to both insulae, a lack of connectivity to dorsal ACC, as well as increased connectivity to thalamus ($p < 0.001$; **Fig 1B)**.

Dorsal attentional network

In healthy controls, functional connectivity analysis with IPS as the seed region showed significant connectivity between the typical DAN regions (Fox *et al.*, 2005; Mantini *et al.*, 2007; Vossel *et al.*, 2014): bilateral frontoparietal regions: IPS, FEF, and dorsolateral PFC. In contrast, mTLE patients demonstrated significantly decreased connectivity to PFC regions, but increased connectivity to parietal areas ($p < 0.001$; **Fig 1C)**.

[INSERT FIGURE 1 HERE]

Within mTLE Group Differences in Spike-Related Functional Connectivity

Default mode network

During the pre-spike period, no significant connectivity pattern with PCC was found, compared to the rest epoch, suggesting that aberrant connectivity to the DMN may play a role in the generation of interictal spikes. During the spike period, mTLE patients engaged the DMN, showing significant functional connectivity between PCC and prefrontal regions, compared to the rest epoch, which was characterized by a lack of connectivity to PFC **(Fig 2A)**.

Salience network

During the pre-spike period, mTLE patients engaged the SN but showed decreased connectivity between the SN nodes, compared to the rest epoch **(Fig 2B),** suggesting that weaker connectivity within the SN may play a role in mediating interictal spikes. During the spike period, no significant connectivity pattern with INS was found, suggesting that the SN is not engaged during the spike period.

Dorsal attentional network

mTLE patients engaged the DAN during both pre-spike and spike periods, but with significant connectivity differences. During the pre-spike period, mTLE patients showed significantly decreased parietal connectivity, compared to the rest epoch, whereas during the spike period, the patients showed similar DAN connectivity to the rest epoch **(Fig 2C)**.

[INSERT FIGURE 2 HERE]

Discussion

The objective of this study was to investigate mTLE-associated alterations in functional connectivity involving three resting state networks: DMN, SN and DAN, and their relationship to both interictal spikes and the pre-spike time epoch. Using simultaneous EEG-fMRI, we expanded on the findings of our previous study (Faizo *et al.*, 2014) in which we demonstrated a loss of bilateral hippocampal connectivity immediately prior to the appearance of interictal spikes. The results of the current study show significant mTLE-related alterations in functional connectivity of all three resting state networks compared to healthy controls. In contrast to the healthy cohort, the resting state networks of mTLE patients are characterized by a lack of or decreased functional connectivity to prefrontal areas and increased connectivity to subcortical and posterior areas. In addition, there are significant differences in functional connectivity of the resting state networks between pre-spike and spike brain states in mTLE. In relation to the pre-spike period, mTLE patients engage the

DAN and SN, but not DMN, and show, in contrast to the rest period, decreases in functional coherence within these networks. In relation to the spike period, mTLE patients engage the DMN and DAN, but not SN, and show, in contrast to the rest period, connectivity to prefrontal areas.

General alterations in resting state networks of mTLE patients

Compared to the healthy participants, all three resting state networks of mTLE patients show significant alterations during rest, both in terms of decreases and increases of functional connectivity between the networks' nodes. Specifically, disturbances in intrinsic activity of mTLE patients include a loss of or decreased connectivity to prefrontal areas, specifically to medial and dorsolateral PFC, and increased connectivity to thalamus and posterior parietal areas. The medial PFC cortex has been implicated in memory, decision-making, and social cognition (Burianova & Grady, 2007; Grossmann, 2013), whilst the dorsolateral PFC is known to subserve complex and sequential brain functions, such as planning, working memory, and response inhibition (Wood and Grafman, 2003). Our findings align with Yuan *et al.* (2013) who have recently reported decreased functional connectivity within the DMN of mTLE patients, and, especially, a lack of connectivity to the PFC. Whether these connectivity alterations reflect the impact of the underlying pathophysiology of mTLE or secondary seizure propagation is still unclear (Devinsky, 2005; Stretton & Thompson, 2012). Available evidence suggests that both mechanisms might be at play, as propagated activity from seizures and interictal spikes over a long period of time may cause significant functional changes in the DMN due to the PFC's connection to the compromised hippocampal complex by a direct neuroanatomical pathway (Thierry *et al.*, 2000). Other researchers have reported decreases in functional connectivity specifically between the hippocampus and PFC in mTLE patients (Pittau *et al* 2012), as well as prefrontal

hypometabolism and hypofunction in patients with intractable mTLE associated with cognitive decline (Takaya *et al.*, 2006).

In the SN, which subserves interoceptive awareness, environmental monitoring, and salient response selection (Taylor *et al.*, 2009), we found decreased functional connectivity between insular cortex and dorsal ACC, extending the recent work by Luo *et al.* (2014) who demonstrated that, in patients with childhood absence epilepsy who suffer from a loss of awareness, inability in identifying and manipulating salient stimuli is associated with abnormal connectivity between the main SN nodes. Our results suggest that, in mTLE patients, the structure and function of the SN might be directly impacted by mTLE-related hippocampal changes via the direct hippocampo-insular pathway, perhaps mediating a decline in associative learning, which is known to be directly proportional to the extent of hippocampal and parahippocampal damage in mTLE patients (Weniger *et al.*, 2004). As such, functional alterations within the SN may underlie specific mTLE deficits in the processing of salient information, such as newness (*e.g.*, detecting a new object in a well-known environment) or associative learning (*e.g.*, pairing between two stimuli).

In the DAN, which subserves goal-directed, top-down attentional processing (Corbetta & Shulman, 2002), we found decreased functional connectivity to PFC; specifically, to DAN's major prefrontal nodes, bilateral FEF, which play crucial role in controlling visual attention and eye movements (Schall, 2004). Our findings support existing behavioural evidence that demonstrates a decline in goal-driven attention during executive and working memory tasks in mTLE patients (Liao *et al.*, 2010, Zhang *et al.*, 2009). We suggest that it is possible that the functional alterations in connectivity to the FEF might be a consequence of long-term injurious effects of seizure propagation throughout this large-scale network (Kaplan, 2005), altering the patient's shift in attention (Nummenmaa *et al.*, 2010). More extensive evidence is needed to support this supposition conclusively; however, a

recent study presents functional coherence of ictal spikes followed by fast rhythmic spikes in the frontal lobes of mTLE patient with epileptic nystagmus (Kim *et al.*, 2013).

In contrast to significant decreases in resting state connectivity, we observed significantly increased connectivity to the thalamus (DMN and SN) and precuneus (DMN and DAN). The thalamus is anatomically connected to the mesolimbic structures, namely the hippocampus, amygdala, and entorhinal cortex (Carlesimo *et al.,* 2011; Swenson, 2006) and the associated thalamo-cortical activity has been implicated in the regulation of consciousness (Min, 2010; Zhou *et al.*, 2011). Both the DMN and SN play a critical role in maintaining consciousness and awareness; as such, disturbances in functional connectivity within these networks might be associated with reductions or loss of awareness during seizures (Craig, 2009; Luo *et al.*, 2014). We suggest that the increased connectivity to the thalamus may serve as a compensatory mechanism that counters the functional alterations within the DMN and SN in mTLE patients. The precuneus, on the other hand, is known to be involved during orienting tasks (Kelley *et al.*, 2008, Yantis *et al.*, 2002) and is anatomically connected to the intraparietal sulcus, an area critically involved in visual and spatial processing (Cavanna and Trimble, 2006). Other cortical and sub-cortical projections to and from the precuneus have been demonstrated, for instance to the thalami (Schmahmann and Pandya, 1990), claustrum, and brainstem (Yeterian and Pandya, 1993). This wide range of connections indicates the importance and complexity of the precuneus in regulating higher cognitive function, although its exact role and mechanism are not fully understood. Its abnormal connectivity to intraparietal sulcus in mTLE patients might, however, suggest compensatory recruitment in response to the lack of functional coherence within the DMN and DAN networks.

Specific mTLE alterations prior to and during interictal spikes

In the DMN of mTLE patients, two main findings were demonstrated in relation to the pre-spike and spike periods. Prior to the interictal spikes, we found evidence of a lack of functional connectivity to the DMN, followed by the re-engagement of the DMN during the spike period, with increases of functional connectivity to the prefrontal cortex. Whilst earlier studies have linked the deactivation of the DMN to the interictal spikes (Fahoum *et al.*, 2012; Laufs *et al.*, 2007), our results specifically isolate these reductions in functional coherence within the DMN to the prespike period. This temporal epoch is likely to be critical to the genesis of spikes. Both SN and DAN were recruited prior to the interictal spikes, but the networks were characterized by significantly reduced functional coherence, compared to the rest period. These findings suggest that decreased functional connectivity in these two networks may play an important role in the generation of interictal spikes. Whilst the SN was deactivated during the spikes, in line with a recent study showing functional disruptions in the SN in relation to interictal spikes in children with intractable focal epilepsy (Ibrahim *et al.*, 2014), the DAN showed increases in functional connectivity comparable to that of the rest period. Together, these findings shed light on the role of oscillatory coherence in large-scale resting state networks in the modulation of interictal epileptiform spikes.

Three limitations of the study are of importance to mention. First, a larger sample size is needed to provide further support for the findings of this study. Despite the relatively small sample size, however, the current study's design and analysis ensure reliable results by including a sufficient amount of datapoints in the analysis and, critically, by utilizing bootstrap resampling, a distribution-independent method of statistical inference, which is especially recommended when the sample size is insufficient (Ader *et al.*, 2008). Second, the inclusion of cognitive metrics that are subserved by the RSNs investigated in this study and delineation of subsequent brain-behaviour relations would strengthen the significance of our findings. Finally, although a standard practice and the investigated resting state networks are

largely bilateral, flipping of the images along the antero-posterior axis to the left in three patients with right hippocampal seizure focus may be improved by future studies in which larger sample size would be attained and laterality would be maintained in separate patient groups.

In conclusion, using simultaneous EEG-fMRI, we investigated alterations in functional connectivity within three resting state networks (DMN, SN, and DAN) of mTLE patients and the relation of the changing connectivity patterns to interictal epileptiform spikes. The findings show that, at rest, all three networks of mTLE patients are characterized by significant alterations in functional connectivity; specifically, a lack of connectivity to prefrontal areas and increased connectivity to subcortical and posterior areas. Importantly, prior to the onset of interictal spikes, mTLE patients showed a lack of connectivity to the DMN and decreased connectivity within the SN and DAN, demonstrating alterations in functional coherence that may be responsible for the generation of epileptiform activity. These functional changes may be related to epilepsy-related cognitive abnormalities, as higher cognitive functions rely heavily on the coordinated activity of all three resting state networks. Critically, the results indicate that mTLE-related functional connectivity disruptions actually occur in the pre-spike period, facilitating the interictal spike itself. This makes physiological sense, as the generated spike might, in fact, be an outcome of this disruption in the hemodynamic resting state pattern.

References

Ader, H.J., Mellenbergh, G.J. & Hand, D.J. (2008). Advising on research methods: A consultant's companion. Huizen, The Netherlands: Johannes van Kessel Publishing.

Andrews-Hanna, J.R., Smallwood, J. & Spreng, N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, *1316*, 29-52.

Avoli, M., Biagini, G. & De Curtis, M. (2006). Do interictal spikes sustain seizures and epileptogenesis? *Epilepsy Currents*, *6*, 203-207.

Beucke, J. C., Sepulcre, J., Eldaief, M.C., Sebold, M., Kathmann, N. & Kaufmann, C. (2014). Default mode network subsystem alterations in obsessive-compulsive disorder. *The British Journal of Psychiatry*, *205*, 376-382.

Biswal, B., Yetkin, F. Z., Haughton, V. M. & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine, 34*, 537-41.

Braakman, H.M., van der Kruijs, S.J., Vaessen, M.J. *et al.* (2012). Microstructural and functional MRI studies of cognitive impairment in epilepsy. *Epilepsia*, *53*, 1690-1699.

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., Hedden, T., Andrews-Hanna, J.R., Sperling, R.A. & Johnson, K.A. (2009). Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience*, *29*, 1860-1873.

Buckner, R. L., Andrews-Hanna, J. R. & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, *1124*, 1-38.

Burianova, H., McIntosh, A.R. & Grady, C.L. (2010). A common functional brain network for autobiographical, episodic, and semantic memory retrieval. *NeuroImage*, *49*, 865–874.

Burianova, H. & Grady, C.L. (2010). Common and unique neural activations in autobiographical, episodic, and semantic retrieval. *Journal of Cognitive Neuroscience*, *19*, 1520-1534.

Carlesimo, G. A., Lombardi, M. G. & Caltagirone, C. (2011). Vascular thalamic amnesia: A reappraisal. *Neuropsychologia, 49*, 777-89.

Cavanna, A. E. & Trimble, M. R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain, 129*, 564-83.

Chen, A.C., Oathes, D.J., Chang, C., Bradley, T., Zhou, Z.W., Williams, L.M., Glover, G.H., Deisseroth, K. & Etkin, A. (2013). Causal interactions between fronto-parietal central executive and default-mode networks in humans. *Proceedings of the National Academy of Sciences, U S A, 110*, 19944–19949.

Corbetta, M. & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*, 201-215.

Craig, A. D. (2009). How do you feel now? The anterior insula and human awareness. *Nature Reviews Neuroscience, 10*, 59-70.

Clemens, B., Puskas, S., Bessenyei, M., Emri, M., Spisak, T., Koselak, M., Hollody, K., Fogarasi, A., Kondakor, I., Fule, K., Bense, K. & Fekete, I. (2011). EEG functional connectivity of the intrahemispheric cortico-cortical network of idiopathic generalized epilepsy. *Epilepsy Research, 96*, 11-23.

Damoiseaux, J. S., Rombouts, S.A.R.B., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M. & Beckmann, C.F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of National Academy of Sciences, USA, 103*, 13848-13853.

Dang, L. C., Donde, A., Madison, C., O'Neil, J. P. & Jagust, W. J. (2012). Striatal dopamine influences the default mode network to affect shifting between object features. *Journal of Cognitive Neuroscience, 24*, 1960-70.

Delorme, A. & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*, 9-21.

Devinsky, O. (2005). The myth of silent cortex and the morbidity of epileptogenic tissue: Implications for temporal lobectomy. *Epilepsy Behaviour, 7*, 383-389.

Dinkelacker, V., Dupont, S. & Samson, S. (2016). The new approach to classification of focal epilepsies: Epileptic discharge and disconnectivity in relation to cognition. *Epilepsy & Behavior, 64*, 322-328.

Efron, B. & Tibshirani, R. (1985). The bootstrap method for assessing statistical accuracy. *Behaviormetrika, 17*, 1–35.

Elton, A. & Gao, W. (2015). Task-related modulation of functional connectivity variabiliy and its behavioral correlations. *Human Brain Mapping, 36*, 3260-3272.

Fahoum, F., Lopes, R., Pittau, F., Dubeau, F. & Gotman, J. (2012). Widespread epileptic networks in focal epilepsies: EEG-fMRI study. *Epilepsia, 53*, 1618-27.

Faizo, N. L., Burianova, H., Gray, M., Hocking, J., Galloway, G. & Reutens, D. (2014). Identification of pre-spike network in patients with mesial temporal lobe epilepsy. *Frontiers in Neurology, 5*, 222.

Fleck, D.E., Shear, P.K. & Strakowski, S.M. (2002). A reevaluation of sustained attention performance in temporal lobe epilepsy. *Archives of Clinical Neuropsychology, 17*, 399–405.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C. & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences, USA, 102*, 9673-9678.

Friston, K. J., Ashburner, J., Frith, C. D., Poline, J. B., Heather, J. D., & Frackowiak, R. S. J. (1995). Spatial registration and normalization of images. *Human Brain Mapping, 3*, 165-189.

Greicius, M.D., Krasnow, B., Reiss, A.L. & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences, U S A, 100*, 253–258.

Grossmann, T. (2013). The role of medial prefrontal cortex in early social cognition. *Frontiers in Human Neuroscience, 7*.

Hufnagel, A., Dumpelmann, M., Zentner, J., Schijns, O. & Elger, C. E. (2000). Clinical relevance of quantified intracranial interictal spike activity in presurgical evaluation of epilepsy. *Epilepsia, 41*, 467-478.

Huijbers, W., Pennartz, C. M., Cabeza, R. & Daselaar, S. M. (2011). The hippocampus is coupled with the default network during memory retrieval but not during memory encoding. *PLoS One, 6*, e17463.

Ibrahim, G. M., Cassel, D., Morgan, B. R., Smith, M. L., Otsubo, H., Ochi, A., Taylor, M., Rutka, J. T., Snead, O. C., 3rd & Doesburg, S. (2014). Resilience of developing brain networks to interictal epileptiform discharges is associated with cognitive outcome. *Brain, 137*, 2690-2702.

Jacobs, J., Levan, P., Moeller, F., Boor, R., Stephani, U., Gotman, J. & Siniatchkin, M. (2009). Hemodynamic changes preceding the interictal EEG spike in patients with focal epilepsy investigated using simultaneous EEG-fMRI. *NeuroImage, 45*, 1220-1231.

Janszky, J., Fogarasi, A., Jokeit, H., Schulz, R., Hoppe, M. & Ebner, A. (2001). Spatiotemporal relationship between seizure activity and interictal spikes in temporal lobe epilepsy. *Epilepsy Research, 47*, 179-188.

Jurcak, V., Tsuzuki, D., & Dan, I. (2007). 10/20, 10/10, and 10/5 systems revisited. Their validity as relative head-surface-based positioning systems. *NeuroImage, 34*, 1600-111.

Kahn, I., Andrews-Hanna, J. R., Vincent, J. L., Snyder, A. Z. & Buckner, R. L. (2008). Distinct cortical anatomy linked to subregions of the medial temporal lobe revealed by intrinsic functional connectivity. *Journal of Neurophysiology, 100*, 129-139.

Kaplan, P.W. (2005). Gaze deviation from contralateral pseudoperiodic lateralized epileptiform discharges (PLEDs). *Epilepsia, 46*, 977-979.

Kelley, T. A., Serences, J. T., Giesbrecht, B. & Yantis, S. (2008). Cortical mechanisms for shifting and holding visuospatial attention. *Cerebral Cortex, 18*, 114-125.

Kim, K. S., Kim, Y. H., Hwang, Y., Kang, B., Kim, D. H. & Kwon, Y. S. (2013). Epileptic nystagmus and vertigo associated with bilateral temporal and frontal lobe epilepsy. *Clinical and Experimental Otorhinolaryngoly, 6*, 259-262.

Kobayashi, E., Bagshaw, A. P., Benar, C. G., Aghakhani, Y., Andermann, F., Dubeau, F. & Gotman, J. (2006). Temporal and extratemporal BOLD responses to temporal lobe interictal spikes. *Epilepsia, 47*, 343-354.

Koshino, H., Minamoto, T., Yaoi, K., Osaka, M. & Osaka, N. (2014). Coactivation of the default mode network regions and working memory network regions during task preparation. *Scientific Reports, 4*:5954.

Krishnan, A., Williams, L. J., McIntosh, A. R. & Abdi, H. (2011). Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. *Neuroimage, 56*, 455-475.

Laufs, H., Hamandi, K., Salek-Haddadi, A., Kleinschmidt, A. K., Duncan, J. S. & Lemieux, L. (2007). Temporal lobe interictal epileptic discharges affect cerebral activity in "default mode" brain regions. *Human Brain Mapping, 28*, 1023-1032.

Liao, W., Zhang, Z., Pan, Z., Mantini, D., Ding, J., Duan, X., Luo, C., Lu, G. & Chen, H. (2010). Altered functional connectivity and small-world in mesial temporal lobe epilepsy. *PLoS ONE*, 5, e8525.

Lin, J.J., Mula, M., Hermann, B.P. (2012). Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. *Lancet, 380*, 1180-1192.

Luo, C., Yang, T., Tu, S., Deng, J., Liu, D., Li, Q., Dong, L., Goldberg, I., Gong, Q., Zhang, D., An, D., Zhou, D. & Yao, D. (2014). Altered intrinsic functional connectivity of

the salience network in childhood absence epilepsy. *Journal of Neurological Science, 339*, 189-95.

Manoliu, A., Riedl, V., Zherdin, A., Muhlau, M., Schwerthoffer, D., Scherr, M., Peters, H., Zimmer, C., Forstl, H., Bauml, J., Wohlschlager, A.M. & Sorg, C. (2014). Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. *Schizophrenia Bulletin*, *40*, 428–437.

Mantini, D., Perucci, M. G., Del Gratta, C., Romani, G. L. & Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. *Proceedings of the National Academy of Sciences, USA, 104*, 13170-13175.

Marsh, E.D., Peltzer, B., Brown III, M.W., Wusthoff, C., Storm Jr, P.B., Litt, B. & Porter, B.E. (2010). Interictal EEG spikes identify the region of seizure onset in some, but not all pediatric epilepsy patients. *Epilepsia*, *51*, 592-601.

Matsumoto, J. Y., Stead, M., Kucewicz, M. T., Matsumoto, A. J., Peters, P. A., Brinkmann, B. H., Danstrom, J. C., Goerss, S. J., Marsh, W. R., Meyer, F. B. & Worrell, G. A. (2013). Network oscillations modulate interictal epileptiform spike rate during human memory. *Brain, 136*, 2444-2456.

McIntosh, A. R. & Lobaugh, N. J. (2004). Partial least squares analysis of neuroimaging data: Applications and advances. *NeuroImage*, *23*, Suppl 1, S250-263.

McIntosh, A. R. & Chau, W.K. & Protzner, A.B. (2004). Spatiotemporal analysis of event-related fMRI data using partial least squares. *NeuroImage, 23*, 764-775.

McIntosh, A.R., Bookstein, F., Haxby, J. & Grady, C.L. (1996). Spatial pattern analysis of functional brain images using partial least squares. *NeuroImage*, *3*, 143–157.

Menon, V. & Uddin, L.Q. (2010). Saliency, switching, attention, and control: A network model of insula function. *Brain Structure & Function*, *214*, 655-667.

Min, B. K. (2010). A thalamic reticular networking model of consciousness. *Theoretical Biology and Medical Modelling, 7*, 10.

Moeller, F., Siebner, H. R., Wolff, S., Muhle, H., Boor, R., Granert, O., Jansen, O., Stephani, U. & Siniatchkin, M. (2008). Changes in activity of striato-thalamo-cortical network precede generalized spike wave discharges. *NeuroImage, 39*, 1839-1849.

Nummenmaa, L., Passamonti, L., Rowe, J., Engell, A. & Calder, A.J. (2010). Connectivity analysis reveals a cortical network for eye gaze perception. *Cerebral Cortex*, *20*, 1780-1787.

Pittau, F., Grova, C., Moeller, F., Dubeau, F. & Gotman, J. (2012). Patterns of altered functional connectivity in mesial temporal lobe epilepsy. *Epilepsia, 53*, 1013-1023.

Pittau, F., Levan, P., Moeller, F., Gholipour, T., Haegelen, C., Zelmann, R. et al. (2011). Changes preceding interictal epileptic EEG abnormalities: Comparison between EEG/fMRI and intracerebral EEG. *Epilepsia, 52,* 1120-1129.

Raichle, M. E., Macleod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A. & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, USA, 98,* 676-682.

Rathakrishnan, R., Moeller, F., Levan, P., Dubeau, F. & Gotman, J. (2010). BOLD signal changes preceding negative responses in EEG-fMRI in patients with focal epilepsy. *Epilepsia, 51,* 1837-1845.

Sambataro, F., Murty, V.P., Callicott, J.H., Tan, H.Y., Das, S., Weinberger, D.R. & Mattay, V.S. (2010). Age-related alterations in default mode network: Impact on working memory performance. *Neurobiology of Aging, 31,* 839–852.

Sampson, P. D., Streissguth, A. P., Barr, H. M., & Bookstein, F. L. (1989). Neuro-behavioral effects of prenatal alcohol: part II. Partial least-squares analysis. *Neurotoxicology and Teratology, 11,* 477-491.

Schall, J. D. (2004). On the role of frontal eye field in guiding attention and saccades. *Vision Research, 44,* 1453-1467.

Schmahmann, J. D. & Pandya, D. N. (1990). Anatomical investigation of projections from thalamus to posterior parietal cortex in the rhesus monkey: A WGA-HRP and fluorescent tracer study. *Journal of Computational Neurology, 295,* 299-326.

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., Reiss, A. L. & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience, 27,* 2349-2356.

Sheline, Y.I., Price, J.L., Yan, Z. & Mintun, M.A. (2010). Resting-state functional MRI in depression umasks increased connectivity beween networks via the dorsal nexus. *Proceedings of the National Academy of Sciences, USA, 107,* 11020-11025.

Spreng, R.N., Sepulcre, J., Turner, G.R., Stevens, W.D. & Schacter, D.L. (2013). Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. *Journal of Cognitive Neuroscience, 25,* 74–86.

Sridharan, D., Levitin, D. J. & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences, USA, 105,* 12569-12574.

Stella, F. & Maciel, J.A. (2003). Attentional disorders in patients with complex partial

epilepsy. *Arquivos de Neuro-psiquiatria, 61*, 335–338.

Stretton, J. & Thompson, P. J. (2012). Frontal lobe function in temporal lobe epilepsy. *Epilepsy Research, 98*, 1-13.

Swenson, R. S. (2006). Limbic System. *In:* Swenson, R. (ed.) *Review of Clinical and Functional Neuroscience*. Dartmouth Medical School: Dartmouth Medical School.

Takaya, S., Hanakawa, T., Hashikawa, K., Ikeda, A., Sawamoto, N., Nagamine, T., Ishizu, K. & Fukuyama, H. (2006). Prefrontal hypofunction in patients with intractable mesial temporal lobe epilepsy. *Neurology, 67*, 1674-1676.

Taylor, K.S., Seminowicz, D.A. & Davis, K.D. (2009). Two systems of resting state connectivity between the insula and cingulate cortex. *Human Brain Mapping, 30*, 2731-2745.

Thierry, A. M., Gioanni, Y., Degenetais, E. & Glowinski, J. (2000). Hippocampo-prefrontal cortex pathway: anatomical and electrophysiological characteristics. *Hippocampus, 10*, 411-419.

Uddin, L.Q. (2015). Salience processing and insular cortical function and dysfunction. *Nature Reviews Neuroscience, 16*, 55-61.

Van Den Heuvel, M. P. & Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology, 20*, 519-534.

Vatansever, D., Menon, D.K., Manktelow, A.E., Sahakian, B.J. & Stamatakis, E.A. (2015). Default mode dynamics for global functional integration. *The Journal of Neuroscience, 35*, 15254-15262.

Vossel, S., Geng, J. J. & Fink, G. R. (2014). Dorsal and ventral attention systems: Distinct neural circuits but collaborative roles. *Neuroscientist, 20*, 150-159.

Ward, A. M., Schultz, A. P., Huijbers, W., Van Dijk, K. R., Hedden, T. & Sperling, R. A. (2014). The parahippocampal gyrus links the default-mode cortical network with the medial temporal lobe memory system. *Human Brain Mapping, 35*, 1061-1073.

Weniger, G., Boucsein, K. & Irle, E. (2004). Impaired associative memory in temporal lobe epilepsy subjects after lesions of hippocampus, parahippocampal gyrus, and amygdala. *Hippocampus, 14*, 785-796.

Witter, M. P., Wouterlood, F. G., Naber, P. A. & Van Haeften, T. (2000). Anatomical organization of the parahippocampal-hippocampal network. *Annals of the New York Academy of Sciences, 911*, 1-24.

Wood, J. N. & Grafman, J. (2003). Human prefrontal cortex: Processing and representational perspectives. *Nature Reviews Neuroscience, 4*, 139-147.

Woodward, N.D., Rogers, B. & Heckers, S. (2011). Functional resting-state networks are differentially affected in schizophrenia. *Schizophrenia Research*, *130*, 86-93.

Yantis, S., Schwarzbach, J., Serences, J. T., Carlson, R. L., Steinmetz, M. A., Pekar, J. J. & Courtney, S. M. (2002). Transient neural activity in human parietal cortex during spatial attention shifts. *Nature Neuroscience, 5*, 995-1002.

Yeterian, E. H. & Pandya, D. N. (1993). Striatal connections of the parietal association cortices in rhesus monkeys. *Journal of Computational Neurology, 332*, 175-197.

Yuan, C., Zhang, Z., Wang, Z., Liao, W., Chen, G., Northoff, G. & Lu, G. (2013). Impaired self-referential processing in mesial temporal lobe epilepsy: A functional MRI study. *Neuroscience Letters, 555*, 187-192.

Zhang, Z., Lu, G., Zhong, Y., Tan, Q., Liao, W., Wang, Z., Wang, Z., Li, K., Chen, H. & Liu, Y. (2010). Altered spontaneous neuronal activity of the default-mode network in mesial temporal lobe epilepsy. *Brain Research, 1323*, 152-160.

Zhang, Z., Lu, G., Zhong, Y., Tan, Q., Yang, Z., Liao, W., Chen, Z., Shi, J. & Liu, Y. (2009). Impaired attention network in temporal lobe epilepsy: A resting FMRI study. *Neuroscience Letters, 458***,** 97-101.

Zheng, J., Qin, B., Dang, C., Ye, W., Chen, Z. & Yu, L. (2012). Alertness network in patients with temporal lobe epilepsy: A fMRI study. *Epilepsy Research*, *100*, 67–73.

Zhou, J., Liu, X., Song, W., Yang, Y., Zhao, Z., Ling, F., Hudetz, A. G. & Li, S. J. (2011). Specific and nonspecific thalamocortical functional connectivity in normal and vegetative states. *Conscious Cognition, 20*, 257-268.

Zhou, J., Greicius, M.D., Gennatas, E.D., Growdon, M.E., Jang, J.Y., Rabinovici, G.D., Kramer, J.H., Weiner, M., Miller, B.L. & Seeley, W.W. (2010). Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain, 133*, 1352–1367.

Figure Captions

FIG 1. Between Groups Comparison: Functional Connectivity During Rest in A) the Default Mode Network; **B)** the Salience Network; **C)** the Dorsal Attentional Network.

FIG 2. Within TLE Patient Group Comparison: Functional Connectivity During Rest, Pre-Spike, and Spike Epochs in A) the Default Mode Network; **B)** the Salience Network; **C)** the Dorsal Attentional Network. For clarity, the rest epoch column is replicated from Figure 1 (right column).

Table 1

PATIENTS	LATERALIZATION	AGE OF ONSET	DURATION (years)	CLINICAL MRI	TOTAL # SPIKES (across 6 runs)
1	R	21	12	HS	47
2	L	20	25	N	none
3	R	14	7	N	none
4	R	21	26	HS	52
5	R	21	2	N	none
6	L	30	25	N	50
7	L	17	6	N	24
8	R	16	14	HS	none
9	L	20	24	N	49
10	L	17	3	N	35
11	L	25	7	N	32
12	L	23	21	N	54
13	R	35	2	N	37
14	L	4	55	N	32
15	L	25	8	N	34

Table 1. Patient clinical details & spike distribution. **R** = right; **L** = left; **HS** = hippocampal sclerosis; **N** = normal; none = no spikes have been identified during EEG-fMRI.