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Homotopic Coupling in Persons with Epilepsy using Movie-driven and Resting-state fMRI

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Abstract

For the 30-40% of persons with epilepsy (PWE) with refractory epilepsy, seizure freedom following surgery is affected by the localization of the epileptogenic zone (EZ). However, functional abnormalities can exist at a distance from the EZ, which may contribute to variable outcomes after surgery. Considering epilepsy as a network disorder (Pittau & Vulliemoz, 2015), and evaluating functional coupling among homotopic brain areas, may help predict cognitive outcomes. Homotopic areas are well connected anatomically and undoubtedly work synchronously to generate cognition. We evaluated 22 persons with focal epilepsy and 24 neurologically healthy controls using fMRI at rest and while watching a brief and engaging audiovisual film clip. The Glasser parcellation (Glasser et al., 2016), a surface-based atlas that divides each hemisphere into 180 cortical regions and 22 functionally distinct sections, was applied and a baseline distribution of homotopic connectivity between pairs of regions and sections was established based on a subset of controls. Regional distribution of homotopic coupling activity was investigated as well as the relationship with performance on neuropsychological measures. We demonstrate the combined utility of resting-state and movie-driven fMRI for detecting homotopic functional coupling abnormalities in persons with refractory temporal lobe epilepsy. In addition, we find evidence of patient-specific and widespread abnormal homotopic functional coupling in PWE within and outside the temporal lobe. Finally, we show that the relationship between homotopic coupling at rest and performance on neuropsychological assessments shows group differences. Our findings supplement evidence of altered functional connectivity in epilepsy using resting-state fMRI and demonstrate how the engaged brain is altered in focal epilepsy.

Keywords: Temporal lobe epilepsy, fMRI, naturalistic stimulation, functional connectivity, homotopic coupling, neuropsychological evaluation

Summary for Lay Audience

42 Canadians are diagnosed with epilepsy every day, and 1 in 3 persons with epilepsy (PWE) do not respond to seizure medication. Although surgical resection of the epileptogenic area is the treatment of choice for individuals with refractory epilepsy, the localization of epileptic activity can be difficult and consequently many individuals suffering from epilepsy have limited treatment options. This research aimed to improve pre-surgical assessment by using movie-driven and resting-state fMRI to identify alterations in homotopic functional coupling in PWE. Homotopic coupling is the functional connectivity between mirroring regions in the brain. Epilepsy is an incredibly diverse disease, and the outcomes of this study help to establish movie-driven fMRI as a technique that enables a patient-centered approach to pre-surgical assessment. We show that alterations in homotopic coupling in individuals with focal epilepsy are evident within and outside the temporal lobe. Furthermore, our results show that movie-driven and resting-state fMRI are differentially sensitive to the detection of homotopic coupling abnormalities in PWE. We find that this combined imaging approach will enhance sensitivity to subtle brain lesions, reduce the need for invasive EEG assessment, and improve the surgical options of individuals with ambiguous epileptic activity. The personal and economic burden of epilepsy is high, and surgery is less costly than ongoing medical care. Improving pre-surgical assessments and identifying connectivity alterations in PWE will enable the identification of brain regions and networks critical to the propagation of this disease and thus improve treatment options and patient outcomes.

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PWE	Persons with epilepsy
EZ	Epileptogenic zone
TLE	Temporal lobe epilepsy
AEDs	Anti-epileptic drugs
EEG	Electroencephalography
MRI	Magnetic resonance imaging
FDG-PET	Fluorodeoxyglucose positron emission tomography
SPECT	Single photon emission computed tomography
iEEG	intracranial electroencephalography
fMRI	Functional magnetic resonance imaging
mTLE	Mesial temporal lobe epilepsy
BOLD	Blood-oxygen-level dependent
DMN	Default mode network
ISC	Inter-subject correlation
DTI	Diffusion tensor imaging
MRS	Magnetic resonance spectroscopy
MTS	Mesial temporal sclerosis
FLAIR	Fluid attenuation inversion recovery
RVDLT	Rey Visual Design Learning Test
CALT	Conditional Associative Learning Test
WAIS-IV	Wechsler Adult Intelligence Scale-Fourth Edition
FDR	False discovery rate
IPS	Intraparietal sulcus
MT+	Middle temporal
VPA	Verbal Paired Associates
WMS-IV	Wechsler Memory Scale-Fourth Edition
RCFT	Rey Complex Figure Test
BNT	Boston Naming Test
PIQ	Performance Intelligence Quotient
FSIQ	Full Scale Intelligence Quotient
WASI-II	Wechsler Abbreviated Scale of Intelligence-Second Edition

Chapter 1

Introduction

1.1 Epilepsy

Each day in Canada an average of 42 people are diagnosed with epilepsy, a serious neurological condition that is characterized by recurrent and unprovoked seizures ("Epilepsy Facts", 2016). Given the varied etiology and behavioural manifestations of this disorder, individualized classification is imperative for guiding effective treatment. This classification includes seizure type, epilepsy type, and syndrome, and causes may be structural, genetic, infectious or metabolic (Thijs et al., 2019). Seizures are precipitated by the excessive and hypersynchronous discharge of neurons in the brain that abruptly alter neurological function, and may be focal and occur in a relatively local area of the brain, or involve both hemispheres and be classified as generalized (Stafstrom & Carmant, 2015). This variation in where epileptic activity originates and spreads throughout the cortex determines the behavioural and cognitive effects and therefore seizure semiology. Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy and is diagnosed when epileptic activity originates in the medial temporal region and leads to changes in responsiveness, memory, language, and posture (Bonelli et al., 2011; Stafstrom & Carmant, 2015). The chronic and unpredictable nature of this disorder leads those with a diagnosis of TLE to face significant social, economic and cognitive strain.

1.2 Presurgical Assessment

TLE is primarily treated with anti-epileptic drugs (AEDs). Often, drugs result in effective seizure management, and persons with epilepsy (PWE) are able to resume their typical daily activities (Morgan et al., 2019). However, 30-40% of PWE are not responsive to AEDs (refractory) and require an alternative treatment approach (Morgan et al., 2019). Refractory TLE

PWE may be eligible for surgery in which the epileptogenic zone (EZ), the area of cortex identified by electroencephalography (EEG) where the generation of seizures originates, is resected (Vega-Zelaya et al., 2015). The eligibility and success of surgery is dependent on the accurate localization of the minimum cortical area that will eliminate seizures when resected. To achieve this, the pre-surgical evaluation must be comprehensive and multimodal, utilizing seizure semiology, EEG recordings, neuropsychological assessment, magnetic resonance imaging (MRI), and when required, fluorodeoxyglucose positron emission tomography (FDG-PET), and single photon emission computed tomography (SPECT) (Ganesan & Ursekar, 2014). EEG recordings confirm the diagnosis of epilepsy by characterizing ictal EEG changes as well as provide a broad localization of abnormal activity (Vakharia et al., 2018). Seizure semiology and neuropsychological assessment can implicate an area of the cortex as distinct types of seizures and cognitive changes can be characteristic of particular regions. Additionally, structural MRI is used to detect abnormal tissue or lesions, such as hippocampal sclerosis or focal cortical dysplasia, which can guide surgical planning (Duncan et al., 2016). Ideally, all these data converge on a single, well-defined EZ.

The pre-surgical evaluation of PWE provides valuable information, but may reveal contradictory or ambiguous findings. For example, not all cognitive changes associated with seizures will have lateralizing value, such impairments may not correspond with EEG changes, and PWE may not have visible cerebral structural abnormalities. Such disparities are clinically meaningful as PWE with a clearly identified EZ are twice as likely to have seizure freedom following surgery (Tellez-Zenteno et al., 2010). Of those who undergo these non-invasive assessments, 25-40% will proceed to surgery and 10-25% will be recommended for invasive intracranial EEG (iEEG; Vakharia et al., 2018). iEEG involves the placement of depth electrodes directly inside the brain of PWE in order to obtain data during spontaneous seizure activity, which can provide indications of the seizure onset area (Lachaux et al., 2003). For some PWE, electrodes can remain in place for several weeks, during which time they are required to stay in the hospital. The placement of electrodes are informed by seizure semiology and scalp EEG recordings, however, they do leave much of the cortex unexplored, potentially limiting the information that can be acquired. Yet, iEEG does provide the opportunity to determine the propagation patterns of epileptic activity, and has been shown to benefit those most who show a lack of congruence between MRI and scalp EEG (Pondal-Sordo et al., 2007). Importantly, iEEG

does pose a significant risk for complications such as intracerebral hemorrhage, scalp infection, cerebrospinal fluid leak and subdural bleeding (Pondal-Sordo et al., 2007). Thus, a non-invasive technique to optimize the presurgical assessment of refractory epilepsy PWE may provide an additional option for the localization of the EZ in order to improve outcomes and increase the number of PWE for whom surgery is an option.

1.3 Epilepsy as a Network Disorder

The traditional model of epilepsy considers a single pathological area that generates seizure activity. Surgical resection of that region is hypothesized to stop seizures and halt the progressive cognitive impairments associated with TLE (Chiang et al., 2015). However, recent evidence strongly suggests that epilepsy can also be caused by dysfunction within an epileptic network (Pittau & Vulliemoz, 2015). This paradigm shift offers a potential explanation for resective surgery that does not always effectively control seizures, despite localization of the EZ (Neal et al., 2020). Epilepsy may be better characterized as abnormal brain activity within a network of cortical and subcortical areas, in addition to the dysfunction of a single pathological area. The epileptic network can be defined as cortical areas which are correlated with the EZ, and/or those that show aberrant patterns of functional connectivity (Marino et al., 2019). Functional connectivity signifies the statistical relationship between neural activity in spatially remote brain areas (Wang et al., 2015). Using functional brain imaging tools such as functional MRI (fMRI) to evaluate functional connectivity can provide important insight into the epileptic network underlying focal epilepsies such as TLE.

1.4 Functional Connectivity Changes in Epilepsy

Mapping and understanding seizure networks is a contemporary focus in epilepsy research and findings highlight functional irregularities within and outside the hypothesized EZ in individuals with TLE. Using resting-state fMRI, Haneef et al. (2015) showed that individuals with TLE demonstrate an overall decrease in the connectivity strength between nodes in the temporal lobe and the rest of the cortex, as well as a progressive reduction in the variability of connections when correlated with epilepsy duration. These findings suggest that the range of

weaker and stronger functional connections is reduced in epilepsy, signifying functional reorganization in response to epileptic activity that is likely dependent on factors such as pathology and time. Notably, such changes in functional connectivity can further characterize individuals with similar seizure types. A connectivity model of mesial TLE (mTLE) was created by identifying the consistent whole brain functional connections in PWE who had been seizure free for one year (Morgan et al., 2019). Comparing the functional networks of PWE with poor postoperative outcomes to this model, connectivity strength and patterns differed significantly in individuals with the same epilepsy classification (Morgan et al., 2019). Therefore, network properties are involved in epileptogenic processes and are likely causally related to patient outcomes. Moreover, such changes have localizing value when comparing the EEG seizure onset area and functional connectivity abnormalities identified using resting-state fMRI. When the spatial concordance of the two were high, PWE showed superior surgical outcomes than those with further functional abnormalities outside the EZ (Lee et al., 2014). Widespread extratemporal involvement is likely more difficult to treat surgically as impaired activity is not regionally constrained. Thus, the identification of altered functional connections outside the EZ may be a useful strategy in the presurgical assessment of PWE.

Individuals with TLE have consistently shown congruent alterations of connectivity patterns including increased connectivity between the occipital gyri (Liu et al., 2016; Wang et al., 2015), medial temporal lobe structures (McCormick et al., 2013; McCormick et al., 2014), and decreased connectivity in the inferior frontal regions (Chang et al., 2019; Liu et al., 2016). Importantly, patterns of functional connectivity have also been shown to be unique at the individual level in TLE. Marino et al., (2019) used iEEG data to map patient-specific epilepsy networks during the interictal period by identifying the connections that were correlated to the seizure onset electrode. When compared between subjects, the topographic distribution of functional connectivity was found to differ, despite anatomical similarities between the EZ. Combining EEG and resting-state fMRI, Neal et al., (2020) also used patient-specific connectivity models and found that connectivity within the voxels of each network were significantly higher in individuals with TLE than controls. In addition, greater surgical disconnection of these epileptogenic networks was strongly associated with postoperative seizure freedom and improved cognitive functioning (Neal et al., 2020). These findings suggest that an individualized understanding of aberrant functional connections may inform surgical planning

and translate to improved outcomes for individuals with poorly localized refractory TLE. Undoubtedly, an evaluation of intra and interhemispheric functional connections between regions beyond those deemed critical to TLE is necessary to better characterize the epileptic network.

1.5 Homotopic Coupling

To some extent, functional connectivity is mediated by structural connectivity, and those regions which are strongly anatomically connected may provide a useful framework for characterizing altered connectivity in TLE. Homotopic coupling is the structural and functional association between mirroring interhemispheric regions and is a fundamental characteristic of the brain's architecture (Mancuso et al., 2019). Robust homotopic activity has been repeatedly observed using resting-state fMRI, and is likely influenced by the high number of callosal fibers connecting homotopic regions in the two hemispheres (Zuo et al., 2010). The corpus callosum is the large bundle of white-matter fibers that mediate the interhemispheric exchange of information (Tzourio-Mazoyer et al., 2016). The enhanced structural architecture between homotopic regions allows for a narrow distribution of typical functional connectivity as those regions close to the midline and connected by stronger and faster corpus callosum fibers show enhanced homotopic coupling, while lateral regions are characterized by weaker homotopic coupling (Mancuso et al., 2019). These well characterized patterns of homotopic coupling enhance the identification of altered connectivity in those with neurologic conditions such as epilepsy. Furthermore, functional connectivity findings of regions that are strongly structurally connected have been found to produce less variable results than those using whole brain functional connectivity analyses (Haneef et al., 2015). Patterns of homotopic connectivity disruptions have been shown in autism (Anderson et al., 2011), depression (Wang et al., 2013), and multiple sclerosis (Zhou et al., 2013), which suggests that interhemispheric connectivity may reflect pathological damages from these conditions. Interhemispheric communication between brain regions is critical for the integration of cognition and behaviour, and yet alterations in the connectivity between homotopic regions is poorly understood in epilepsy. This is especially important given that seizures are not only the result of an excitatory and inhibitory neuronal

imbalance, but also the modification of mechanisms supporting neural synchrony (Bettus et al., 2009). Additionally, having a corpus callosotomy has been shown to decrease the frequency of seizures (Jenssen et al., 2006) and normalize altered interhemispheric functional connectivity (Pizoli et al., 2011). These findings suggest that epileptogenic networks may involve areas contralateral to the EZ and neural changes in epilepsy can result in interhemispheric functional connectivity alterations.

Studies documenting altered connectivity in PWE largely focus on intrahemispheric connectivity. For example, increased connectivity has been documented between the bilateral cuneus and anterior cingulate cortex, and decreased connectivity was found between the inferior frontal gyrus and temporal pole in individuals with TLE (Ji et al., 2014). There has been less focus on the functional connectivity between homotopic regions in epilepsy, particularly in those outside the temporal lobe. mTLE has been associated with impaired connectivity within and between hippocampi (Pereira et al., 2010). Additionally, decreased homotopic connectivity has been observed in the temporal pole, amygdala, insula and putamen, suggesting that changes in the temporal lobe likely alter connectivity with the contralateral regions (Xu et al., 2014). Yang et al., (2014) found a significant increase in the connectivity of the bilateral anterior cingulate and medial prefrontal cortex in individuals with generalized tonic-clonic seizures. Furthermore, homotopic functional connectivity in the bilateral thalamus, cerebellum and orbital frontal cortex was negatively correlated with illness duration. These results suggest that prolonged epileptic activity escalates changes in interhemispheric communication. It has been demonstrated that individuals with more widespread homotopic connectivity differences had less favourable surgical outcomes in terms of seizure freedom (Xu et al., 2014). Notably, neurotypical individuals show consistent patterns of regional variation in the strength of homotopic functional connectivity that is compatible with models of hemispheric specialization (Hervé et al., 2013). Specifically, there is weaker resting-state connectivity between homotopic prefrontal and temporoparietal areas while the sensorimotor cortex elicits stronger connectivity (Zuo et al., 2010). As functional homotopy is seemingly tied with cognition, it is important to explore the homotopic connectivity of regions within and outside of the temporal lobe and explore the potential effects on cognitive function.

1.6 Neuropsychological Assessment

The cognitive and behavioural expressions of neural changes in epilepsy require comprehensive neuropsychological assessments. Intellectual functioning, visual-spatial skills, language, executive functions, motor functions, and memory are typically evaluated (Lezak et al., 2012). The observation of characteristic changes in cognitive function can contribute to the classification of TLE. Selective impairment in episodic memory tasks is common, the content of which can provide lateralizing information that may localize the hemisphere of the EZ (Lezak et al., 2012). Specifically, deficits in verbal memory is indicative of a left hemispheric focus, while visuospatial memory impairments are common in those with right hemispheric localization (Milner, 1972). Furthermore, regardless of a particular hemispheric focus, TLE patients often show impairment in detailed autobiographical memory retrieval (McAndrews & Cohn, 2012). In individuals with medically refractory epilepsy, the effect of constant and uncontrolled epileptic activity puts them at particular risk of neuropsychological decline, with poor cognitive outcomes observed in 20-25% of PWE (Hermann et al., 2006). It is imperative to characterize the nature and severity of cognitive impairment in TLE patients to inform surgical planning, with greater preoperative capacity associated with greater decline (Chelune, 1995). In TLE, the potential of the resection of anterior and medial temporal lobe structures to control seizures must be balanced with the effects on post-surgical cognition (Barnett et al., 2017). Neuropsychological investigations are critical for identifying candidates for surgery, pre-surgical planning, and the implementation of post-surgical rehabilitation (Lezak et al., 2012).

1.7 Functional Connectivity and Cognition

The interaction of abnormal neural activity and cognitive functioning is complex in epilepsy as PWE with congruent localization of the EZ will still vary in the extent of their cognitive impairments. This disparity likely rests on abnormalities in the epileptic network as healthy cognition is dependent on connectivity within and between multiple brain regions (Wang et al., 2015). Cognitive impairment in epilepsy is traditionally understood in terms of structural deficits, although the functional connections that sustain the epileptogenic network in PWE with

refractory TLE may also contribute to cognitive impairments (Tailby et al., 2018). Alternatively, these changes may be evidence of neural reorganization and serve as a compensatory strategy to maintain healthy cognitive functioning. For example, a positive relationship was demonstrated between working memory scores and functional connectivity in PWE (Bettus et al., 2009). Further, connectivity between the non-pathological medial temporal lobe and frontal cortex also showed a positive relationship with the delayed recall of non-verbal stimuli (Bettus et al., 2009). Similar results were found by McCormick et al., (2013): stronger connectivity between the posterior cingulate cortex and the hippocampus on the epileptogenic side was associated with stronger material-specific memory capacity, as well as postsurgical memory decline. Assessing the relationship between connectivity changes and cognitive function should be a consideration in the pre-surgical assessment of PWE.

Neuropsychological predictions regarding brain-behaviour relationships do not currently consider the role of functional networks that may generate and contribute to the decline of cognitive function. Warren et al., (2017) reasoned that such predictions may be inadequate when the region in question is a "hub", which can be defined as cortical areas that are shown to have connections to multiple brain systems and are especially important for maintaining overall network function. Findings showed that the neuropsychological deficits of PWE with lesions to such areas surpassed expectations and the deficits of PWE with lesions in less connected regions were consistent with neuropsychological evaluations (Warren et al., 2017). These results suggest that brain regions which participate in many functional brain networks may support normal cognitive functioning more so than those with few connections. This is not to say that investigations of functional connectivity diminish the clinical value of neuropsychological evaluations. Rather, such techniques can enhance the role of traditional and novel assessments in the clinical management of PWE. Evidence is growing that documents the relationship between cognitive impairments in TLE and functional connectivity abnormalities outside the EZ. Doucet et al., (2013) showed connections in the medial brain regions outside the temporal lobe were significantly related to episodic memory performance. Thus, a more comprehensive understanding of the neurological basis of cognitive strengths and weaknesses in epilepsy and valid methods for evaluating these is imperative. fMRI is a promising tool for exploring this relationship through an analysis of homotopic connectivity alterations and an enhancement of the role of neuropsychological tests in pre-surgical evaluation.

1.8 Functional Magnetic Resonance Imaging

The role of brain imaging in the clinical management of epilepsy has continuously evolved and today both MRI and fMRI play an essential role in presurgical assessment. MRI is used to identify structural abnormalities in the cerebral cortex that are the likely origin of epileptic activity, which is more likely in individuals with focal seizures or abnormal neurologic findings (Stafstrom & Carmant, 2015). In PWE with negative MRIs or when other methods are necessary to localize the EZ, fMRI is used to map cognitive functions, most commonly language, and identify critical structures that might constrain the surgical approach (Duncan et al., 2016). fMRI detects and localizes neuronal activation through the blood-oxygen-level dependent (BOLD) response, as activation is coupled with an increase in regional blood flow and oxygenated-hemoglobin, and a decrease in deoxygenated-hemoglobin. Oxygenated hemoglobin is magnetically neutral and deoxygenated hemoglobin disrupts the magnetic field of the scanner, producing changes in the MR signal that results in T2 shortening and the hemodynamic response, which plateaus if neuronal activity continues and falls if it stops. Thus, the MRI is able to detect the contrast between active and inactive cortical regions (Becker et al., 2009).

Traditionally, the Wada procedure is used to determine language lateralization in the presurgical assessment of PWE by deactivating one hemisphere using sodium amytal to assess the capacity of the contralateral hemisphere (Szaflarski et al., 2017). Recently, however, a panel of the American Academy of Neurology evaluated the capability of fMRI to determine lateralization and predict postsurgical cognitive outcomes in PWE, in comparison to the Wada procedure. It was concluded that fMRI is an excellent and non-invasive approach for predicting changes in verbal memory, as well as identifying material specific memory abilities associated with the left and right hemisphere (Szaflarski et al., 2017). Thus, the role of fMRI in the diagnosis and surgical planning of PWE can grow to assess the overlap of the EZ with functionally rich cortex implicated in specific cognitive functions. Task-activation paradigms in fMRI have shown some success in assessing the relationship between hemispheric activation during language and memory tasks and performance on cognitive assessments (Cano-López et al., 2018). However, task activation paradigms require longer scans with multiple runs to obtain reliable data. Furthermore, the degree of functional reorganization that some PWE experience

(Powell et al., 2007), has implications for the region of interest approach in these paradigms. Individuals may use alternate strategies or activate varying networks during a task as a result of prolonged epileptic activity, which alters the networks and regions that are typically associated with a memory or language task (Barnett et al., 2017). Alternate fMRI paradigms may provide a greater insight into the overall functional capacity of the neural systems that are tied to the perpetuation of epileptic activity and the associated effects on cognition.

1.9 Resting-state fMRI

Resting-state fMRI detects regional variation in functional connectivity in spontaneous BOLD signals occurring in a resting or task-free state (Wang et al., 2015). While not currently used in clinical practice, resting-state fMRI has been used to compare different epilepsy patient populations with healthy controls to understand how this disorder affects the intrinsic relationships between cortical regions. Specifically, alterations in the brain's default mode network (DMN) have been explored in epilepsy. The DMN is a network of activity that is detectable at rest and consists of bilateral cortical areas in the medial and lateral parietal and temporal, and medial prefrontal cortices (Raichle et al., 2015). At rest, there is evidence that functional abnormalities in TLE are not limited to the EZ, but can be observed in diverse locations throughout the cortex. Utilizing resting-state fMRI to understand the epileptic network has provided important information and helped to evolve the role that brain imaging can play in the presurgical assessment of PWE.

The DMN is of particular relevance in TLE as two nodes of the network, the hippocampus and posterior cingulate cortex, are within the temporal lobe and are strongly associated with memory recognition and recall tasks (Barnett et al., 2017). McCormick et al., (2013) found reduced overall connectivity to the pathological hippocampus and increased connectivity within the homotopic region. This stronger connectivity was found to reflect a compensatory strategy, with memory function improving postoperatively while stronger connectivity in the pathological region was associated with better presurgical memory and greater postsurgical decline (McCormick et al., 2013). A subsequent study replicated these results with additional regions within the DMN, showing that stronger memory abilities were

associated with increased posterior and interhemispheric connectivity (McCormick et al., 2014). Such results have been shown in both resting-state and task-based fMRI, which suggests that interhemispheric connectivity reflects a change in the memory network of individuals with TLE that is protective to the damage on cognition of prolonged epileptic activity. However, there are some inconsistent results in the evaluation of the DMN in epilepsy, likely resulting from heterogeneous groups of PWE and the application of diverse analysis methods. Furthermore, the influence of AEDs and duration of epilepsy vary significantly in seemingly homogenous clinical populations (Gao et al., 2018). It is important to note that resting-state connectivity may show greater sensitivity to variables that interfere with image acquisition, specifically motion, which posits a challenge for the interpretation and generalization of results (Barnett et al., 2017). Additionally, while the exploration of the relationship between functional connectivity and cognition in resting-state has yielded important findings, resting-state activation is not representative of active cognition. The inferences we can make based on resting-state data are limited, as the activation is not driven by a task. Thus, the application of brain imaging techniques that are not as one-dimensional as task-based paradigms but generate more ecologically valid cognition can be valuable for exploring this important relationship in epilepsy.

1.10 Naturalistic Stimulation

Cognitive neuroscience and neuropsychology have typically focused on the use of simple, unimodal tasks to assess isolated behavioural or cognitive constructs in order to relate them to discrete cortical regions (Sonkusare et al., 2019). However, we do not interact with simplified stimuli such as pictures or tones in everyday life, and as such the brain activity inferred from such tasks are not wholly representative of the complex networks that support integrative perceptual experiences. Therefore, evaluating neural processing and cognitive networks during natural, dynamic conditions may enable a more comprehensive understanding of healthy and pathological brain function. Naturalistic paradigms use rich, multisensory dynamic stimuli that represent lived experiences, such as movies, spoken stories, or news articles (Sonkusare et al., 2019). Recent evidence suggests that the brain may be more responsive to naturalistic stimuli. In comparing facial motion and static faces, Schultz and Pilz (2009)

demonstrated that the use of dynamic stimuli elicited higher responses in static-face-sensitive regions. Furthermore, neuronal responses are hypothesized to be more reliable under naturalistic stimulus conditions than under laboratory conditions using artificial stimuli (Hasson et al., 2010). Using fMRI, the use of naturalistic stimulation addresses the limitations inherent in task-based and resting-state designs. Namely, the inferences that can be made are limited to the nature of the task, or in resting-state, to features of functional connectivity that are not actively involved in hierarchical neural systems. Eliciting active and natural neuronal responses, which are not tied to a specific task meant to constrain cognition, provides a novel way of evaluating homotopic functional coupling changes in PWE and the relation of such connections to cognitive functioning.

Free-viewing an engaging audiovisual film clip while undergoing fMRI elicits highly significant and widespread correlations between the brain activity of different people (Hasson et al., 2004). An analytical technique known as inter-subject correlation (ISC) is used to correlate activation across time between subjects. Specifically, the results show that when naturally viewing a film clip, participant's individual brains synchronized highly during emotionally arousing scenes, and in particular brain regions. Namely, primary and secondary visual and auditory areas, as well as association cortices such as the superior temporal sulcus and lateral septum show low intersubject variability (Hasson et al., 2004). Hasson et al., (2008) also explored the similarity of neural responses during movie-viewing and found high synchronization of cortical activity in 45% of the neocortex, which was consistent with eye movement ISC. These results suggest that viewers of highly engaging audiovisual film clips share similar experiences and this technique can be used to identify differences in neuronal responses in different populations. Further, regional variation is evident in this synchronized effect that reflects the regions of the brain that show highly reliable activity between people, and those that show individual variation (Hasson et al., 2004). These patterns allow activation over time to be defined and related to cognitive functioning in order for areas of altered functional connectivity to be localized in PWE and aid in the assessment of the EZ. Importantly, this approach surpasses the ability of resting-state fMRI to capture functional connectivity changes that are critical for cognitive functioning, as variability between people is reduced, potentially increasing sensitivity.

While often used together in the pre-surgical assessment of epilepsy patients, fMRI and neuropsychological assessments are regarded as distinct tools. However, their integration will allow for a deeper understanding of brain-behaviour relationships in epilepsy as the imaging data will be directly related to the stimuli in neuropsychological assessments. Movie-driven fMRI allows for such integration as questions assessing memory can be directly related to the film participants watch in the scanner. Traditionally, unimodal neuropsychological tests are used to assess memory function and have proven to be influential in the neuropsychological understanding of TLE. Specifically, seminal papers regarding cognitive outcomes after epilepsy surgery informed our understanding of the segregation of verbal and non-verbal forms of memory and their localization to the light and right hippocampi, respectively (Scoville and Milner, 1957; Penfield and Milner, 1958). However, to better understand the impact of memory impairment on daily living, we need to move beyond simplified, unimodal stimuli which are not representative of typical and complex memory tasks. This advancement is critical as current assessments are limited in their predictive capacity for how an individual will function in daily life. To address this lack of generalizability, the application of complex and lifelike scenarios to measure cognitive decline should be explored.

1.11 The Current Study

The current study will explore the application of movie-driven fMRI and related movie memory testing as a potential clinical tool for investigating the relationship between homotopic functional connectivity and cognition in TLE. Extensive knowledge has been gained about the epileptic network using iEEG (Marino et al., 2019), resting-state fMRI (Zhou et al., 2013), EEG (Bernasconi et al., 2010) and diffusion tensor imaging (DTI) (Ji et al., 2014). To expand our understanding of how neuronal connections are altered in epilepsy, movie-driven fMRI provides a novel and ecologically valid way to assess natural and dynamic brain function. Given the sensitivity to individual differences movie-driven fMRI has, it is hypothesized that this approach will be more sensitive to differences in homotopic functional connectivity in PWE compared to resting-state fMRI. While interhemispheric connectivity changes have been documented in PWE, relatively little work has been done on homotopic connectivity, despite it being a part of the

fundamental architecture of the brain. Additionally, the literature exploring functional connectivity alterations in TLE is largely limited to regions in the temporal lobe. Thus, the current study aims to provide a whole-brain documentation of homotopic connectivity abnormalities.

The hypothesized utility of functional connectivity in epilepsy is dependent on its relationship with cognitive functioning. Whereas many studies have investigated the relationship between functional and structural connectivity (Ji et al., 2014; Chang et al., 2019), the link to cognition, particularly with homotopic functional connectivity, is relatively unexplored. In the current study we address this gap to examine how alterations in homotopic functional connectivity are related to cognitive deficits as documented by traditional neuropsychological assessments and a movie-memory test that corresponds to the stimuli in the movie-driven fMRI, which has been validated for use in PWE with TLE (Ladowski, 2019).

The majority of research investigating functional connectivity differences in PWE is concerned with group-level differences between healthy controls and PWE, or right versus left localization (Marino et al., 2019). However, an examination of connectivity profiles at the individual level is necessary when exploring a potential pre-surgical evaluation tool, and may be more clinically meaningful. Thus, the aim of this study is to identify whether PWE show altered homotopic functional coupling when compared to healthy controls, as well as identify each patient's homotopic connectivity profile.

This study aims to answer if homotopic functional connectivity alterations are present in PWE, and if there is a relationship between homotopic functional connectivity and performance on neuropsychological cognitive assessments. Furthermore, it is our aim to determine if movie-driven fMRI and a related movie-memory test are able to provide a more sensitive identification of functional connectivity abnormalities and their relationship to cognition than resting-state fMRI.

In the current study, PWE with TLE and age-matched healthy controls were scanned at rest and while watching an edited 8-minute suspenseful clip of Alfred Hitchcock's T.V. episode, "Bang! You're Dead". The clip, previously used in fMRI studies (Naci et al., 2014; Shafto et al., 2014) has been shown to elicit widespread synchronous activity across participants. Participants then completed a range of neuropsychological measures of intelligence, memory and executive function, as well as a movie-memory test relating to the edited film they watched in the scanner.

A surface-based atlas, the Glasser parcellation, was applied to delineate each hemisphere into 180 cortical areas on the basis of similarity in cortical structure and function (Glasser et al., 2016). These regions were identified based on changes in cortical architecture, function, connectivity, and topography in 210 healthy young adults. Additionally, these 180 cortical areas can also be grouped into 22 distinct sections based on common properties including architecture, task-fMRI profiles, and functional connectivity (Glasser et al., 2016). Applying a parcellation that is based on the correspondence between a large number of people and a replication sample, and is informed by cortical thickness, myelin concentration, as well as functional connectivity, allows us to explore functionally distinguishable areas that may be important for cognition. 180 homotopic coupling values were calculated between each region and section and its homotopic pair. In this study, we addressed the following hypotheses: (1) there are measurable differences in homotopic functional connectivity between PWE and healthy controls (2) Movie-driven fMRI would be more sensitive to detecting homotopic coupling abnormalities than resting-state fMRI (3) Abnormal coupling values in PWE would show widespread regional variation and (4) there will be a significant relationship between homotopic coupling and performance on neuropsychological assessments and the movie-memory test. If brain network organization can translate into clinical practice, then changes in homotopic coupling should influence cognition in measurable ways.

Chapter 2

Methods

2.1 Participants

Twenty-two persons with refractory TLE (10 female, mean age 36.64; Table 2-1) who were being evaluated for temporal-lobe resectional surgery to control seizures, were recruited from the Adult Epilepsy Service, University Hospital, London. Age of onset and medication records were collected from each patient's medical record. Further, clinical reports including EEG recording, 891.5 Tesla MRI, PET, magnetic resonance spectroscopy (MRS), and neuropsychological evaluation were obtained, when available. This information was used to localize the epileptogenic lesion. Twenty-four neurologically healthy controls were recruited from the London community and were approximately matched to participants with TLE on sex, handedness, and years of education (14 female; mean age 35.63; Table 2-1). All control participants self-identified as native English speakers and reported no history of psychiatric illness, neurological disorder, or hearing impairment. All participants provided informed consent, and ethical approval was acquired from the Health Sciences Research Ethics Board of the University of Western Ontario (see Appendix A).

Table 2-1

Participant Characteristics

	HC	TLE
n	24	22
Sex (F:M)	14:10	10:12
Age (M ± SD)	35.63 ± 14.99	36.64 ± 13.83
Years of Education (M ± SD)	14.74 ± 1.86	13.91 ± 2.41
Seizure Lateralization		12 L; 8 R; 2 BL
Evidence of MTS on MRI		8 Y; 14 N
Age of Onset (M ± SD)		17.14 ± 13.17
Epilepsy Duration (M ± SD)	.	17.36 ± 15.77

Note. HC = healthy controls demographically matched to TLE sample; TLE - temporal lobe epilepsy patient sample; F = female; M = male; L = left; R = right; BL = bilateral; MTS = mesial temporal sclerosis; MRI = magnetic resonance imaging.

2.2 Procedure

Prior to scanning, healthy controls completed a medical history and medication log. PWE completed a medical history and medication log, as well as measures of depression (Rush et al., 2003), anxiety (Leon et al., 1997), psychological symptoms (Derogatis et al., 1993), sleep quality (Buysse et al., 1989), stigma (Dilorio et al., 2003), disability (Leon et al., 1997) and quality of life (WHOQOL Group, 1998; Cramer et al., 2003). In accordance with the Eplink protocol (Ontario Brain Institute), volume acquisitions for healthy controls and PWE included: T1-weighted structural MRI, fluid attenuation inversion recovery (FLAIR) MRI, MRS, and DTI, followed by 2 runs of functional MRI in a 3 Tesla Siemens Prisma MR imaging system. fMRI data collected included a 6 minute 33 second resting-state imaging (with eyes closed) in accordance with Eplink Protocol II, with three PWE completing 8 minutes of resting-state imaging in accordance with EpLink Protocol III. (Details of image acquisition are given in the next section.) Resting-state imaging for healthy controls and PWE was followed by an 8-minute

scan during which participants watched an audiovisual film clip projected on a mirror box in the scanner. The film clip used was a short, engaging and suspenseful edited version of a half-hour (22-minute) television episode entitled “Alfred Hitchcock Presents: Bang! You’re Dead,” (1961), which has been used previously and been shown to elicit reliable and widespread cortical activity (Hasson et al., 2008; Naci et al., 2014). Participants used MR-compatible headphones (Sensimetrics, S14; www.sens.com) for sound delivery during the film clip, and a sound test was completed prior to scanning. Prior to entering the scanner, participants were told they would be shown a short film clip and were instructed to watch carefully and follow the plot as they would any other television episode or movie.

Following the scan, all participants completed a memory test based on the content of the clip, which included familiarity, timeline and comprehension questions, which have been validated for use with TLE patients (Ladowski, 2019). Healthy controls and PWE then completed several standardized neuropsychological assessments of learning and memory. Specifically, participants completed the Names and Doors subtests of the Doors and People Test (Baddeley et al., 2006), the Rey Visual Design Learning Test (RVDLT; Spreen and Strauss, 1991), and the Conditional Associative Learning Test (CALT; Petrides, 1985). The neuropsychological data for PWE also included results from their neuropsychological evaluation as part of their treatment at the Adult Epilepsy Service. Healthy control participants also completed the Matrix Reasoning and Vocabulary subtest of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler, 2008) as measures of nonverbal/fluid intelligence and crystallized intelligence, respectively. The completion of these assessments took approximately 1 hour 20 minutes to complete. This study reports analyses of the resting-state and movie-driven functional imaging, with the acquired T1 weighted structural MRI used for image registration and localization. The available data for all participants is outlined in Table 2-2, with data indicated with an asterisk used for the purposes of the current study.

Table 2-2

Study Procedures

Participant Group	Neuroimaging	Neuropsychological Tests	Questionnaires
HC	Movie-driven fMRI* Resting-state fMRI*	Movie-memory test*, Names Test*, Doors Test*, Conditional Associative Learning Test*, Rey Visual Design Learning Test*, Matrix Reasoning*, Vocabulary*	Medical History, Medication Log
TLE	Movie-driven fMRI* Resting-state fMRI*	Movie memory test*, Names Test*, Doors Test*, Conditional Associative Learning Test*, Rey Visual Design Learning Test*, Matrix Reasoning*, Vocabulary*, Logical Memory*, Verbal Paired Associates*, Faces*, Family Pictures*, California Verbal Learning Test*, Rey Auditory Verbal Learning Test, Rey Complex Figures Test*, Boston Naming Test*, Animals*, Design Fluency*, Verbal Fluency Test*, WASI-II/WAIS-IV*.	The Quick Inventory of Depressive Symptoms – Self Report, The World Health Organization Quality of Life, The Brief Symptom Inventory, The Generalized Anxiety Disorder Scale, The Sheehan Disability Scale, The Pittsburgh Sleep Quality Index, The Quality of Life in Epilepsy-31, The Epilepsy Stigma Scale, Medical History, Medication Log

2.3 Image Acquisition Eplink Phase II

Imaging was performed using a 3T Siemens Magnetom Prisma scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. An anatomical volume was obtained using a T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (TR = 2300 ms, TE = 2.98 ms echo time, flip angle = 9°, FOV = 256 mm^2, voxel size = 1 x 1 x 1 mm). Functional images were acquired using a gradient echo (GRE) echo planar imaging sequence (TR = 2000 ms, TE = 30 ms echo time, flip angle = 75°, FOV = 192 mm^2, voxel size = 3 x 3 x 3 mm). The scanned volume included 33 slices of 3 mm thickness, collected in interleaved descending order with an interslice gap of 25%. The resting-state run comprised 172 scans and the movie run comprised 246 scans.

2.4 Image Acquisition Eplink Phase III

Imaging was performed using a 3T Siemens Magnetom Prisma scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. An anatomical volume was obtained using a T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (TR = 2300 ms, TE = 2.98 ms echo time, flip angle = 9°, FOV = 256 mm^2, voxel size = 1 x 1 x 1 mm). Functional images were acquired using a gradient echo (GRE) echo planar imaging sequence (TR = 1250 ms, TE = 39 ms echo time, flip angle = 50°, FOV = 220 mm^2, voxel size = 2.5 x 2.5 x 2.5 mm). The scanned volume included 60 slices of 2.5 mm thickness, collected in interleaved descending order with an interslice gap of 25%. Both the resting-state and movie run comprised 246 scans.

2.5 Imaging Preprocessing

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 1.3.2 (Esteban et al., 2018a; Esteban et al., 2018; RRID:SCR_016216), which is based on *Nipype* 1.1.9 (Gorgolewski et al., 2011; Gorgolewski et al., 2018; RRID:SCR_002502) (see Appendix

B). First, the T1-weighted image was corrected for intensity non-uniformity and used as a T1 weighted reference for the rest of the preprocessing. Next, the T1-weighted reference was skull-stripped and spatial normalization was performed. Brain tissue segmentation of cerebrospinal fluid, white-matter, and gray-matter was performed. For both resting-state and movie-viewing scans, functional data preprocessing was performed. A BOLD reference volume and its skull-stripped version were generated and then co-registered to the T1-weighted reference. Next, BOLD runs were slice-time corrected and resampled to Freesurfer space and onto their original, native space and corrected for head-motion and susceptibility distortions. Removal of motion artifacts using independent component analysis was performed on the resampled BOLD time-series after the removal of non-steady state volume and spatial smoothing with an isotropic, Gaussian kernel of 6mm full-width half-maximum. The BOLD time-series were then resampled into MNI standard space. Physiological regressors were extracted as well as three global signals within the cerebral spinal fluid, the white matter, and whole-brain masks, and principal components were estimated after high-pass filtering the preprocessed BOLD time-series.

2.6 Analysis

The goals of the following analyses were to 1) determine whether functional connectivity between homotopic regions differed in PWE compared to demographically matched control participants, 2) establish if abnormalities in homotopic functional coupling in PWE existed within and/or beyond the temporal lobe, and 3) to explore the relationship between homotopic functional coupling and cognitive functioning. Importantly, all analyses were carried out using resting-state and movie-driven fMRI data to determine the nature of the difference between two functional imaging paradigms as it relates to homotopic functional coupling and cognitive performance. Functional connectivity analyses on both resting and movie data were conducted using MATLAB 2018b (Mathworks, Natick, MA, USA) and IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA).

2.7 Parcellation

The preprocessed imaging data were transformed from FreeSurfer space into the Human Connectome Project Space in order to be parcellated. Through this process, the brain was

segmented into grey and white matter, and the cortex was mapped onto a surface, where each vertex of the surface represents a data point. With the imaging data in the correct space, the Glasser parcellation was applied (Glasser et al., 2016). The Glasser parcellation is a surface-based atlas that divides each hemisphere into 180 cortical regions, which can then be grouped into 22 distinct sections based on common properties including architecture, task-fMRI profiles, and functional connectivity (Glasser et al., 2016; see Appendix C). The time courses of all the vertices corresponding to a cortical region were used to form one average time course for that region (see Figure 2-1). The average level of activation was calculated for each region, and Fisher-z transformed Pearson correlation coefficients were calculated between each pair of regions. This process was completed for both resting-state and movie-driven fMRI to determine the 180 homotopic coupling values for each participant corresponding to each region, as well as 22 homotopic coupling values for each participant corresponding to each section.

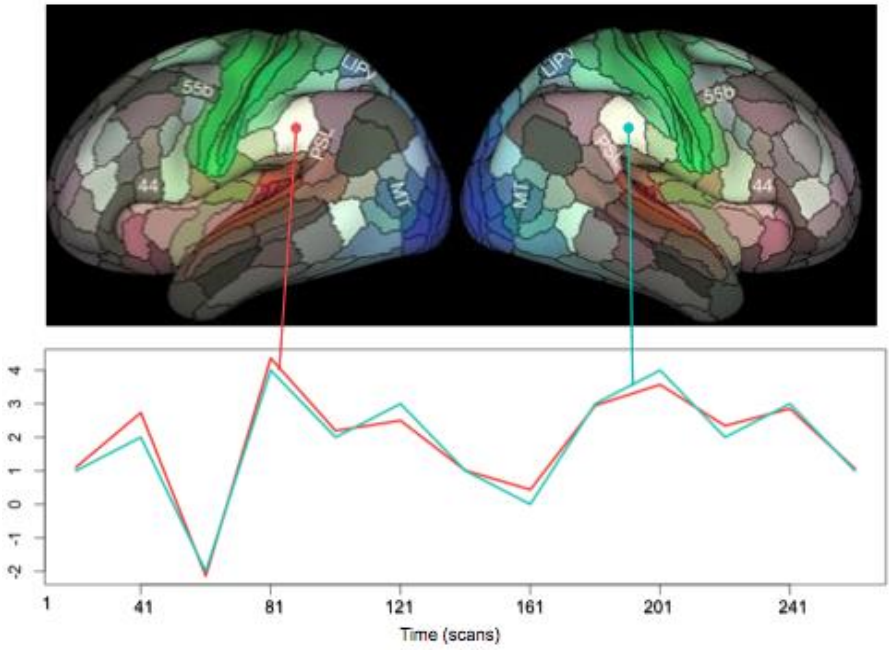

Figure 2-1. *Homotopic Coupling Using the Glasser Parcellation* (Glasser et al., 2016). Homotopic coupling is the correlation between time-course activation in homologous regions of the left and right hemisphere.

2.8 Homotopic Coupling Abnormalities

To determine whether sensitivity to homotopic functional coupling alterations differed between resting-state and movie-driven fMRI, the homotopic coupling value for each of the 180 pairs of regions in PWE were compared to those for the neurological normal control sample. Homotopic coupling values in the healthy control sample were used to create a baseline distribution of coupling activity for each region. The homotopic coupling value for each patient in each region was compared to the corresponding distribution and values above or below two standard deviations from the mean, were identified as outliers, reflecting altered homotopic coupling. The total number of homotopic coupling abnormalities identified in PWE in the movie and resting-state were compared using an independent-samples t-test.

Next, it was important to determine that the abnormal homotopic coupling seen in PWE was greater than what would be found in a sample of neurologically healthy adults. Thus, in both resting-state and movie-driven fMRI, the number of homotopic coupling abnormalities was compared between PWE and healthy controls. Healthy controls were randomly divided into two groups, and a baseline distribution of coupling values for each of the 180 paired regions was created using control group 1. The coupling values for each of the 180 paired regions in PWE and control group 2 were compared to these distributions, and the number of homotopic coupling abnormalities were calculated. Then, control group 2 was used to establish the baseline distribution of coupling values for each of the 180 paired regions and the coupling values for each of the 180 paired regions control group 1 and PWE were compared to these distributions, and the number of homotopic coupling abnormalities was calculated. Given the small sample size used to establish this baseline distribution (n = 12), this process was replicated 500 times, with each iteration generating a new control group 1 and 2 (see Figure 2-2). The average number of identified homotopic coupling abnormalities across all iterations was calculated for each participant. We performed a 2x2 mixed analysis of variance (ANOVA) in SPSS to evaluate changes in homotopic coupling abnormalities with scan type as the within groups factor (movie vs rest) and group as the between-groups factor (patient v. control).

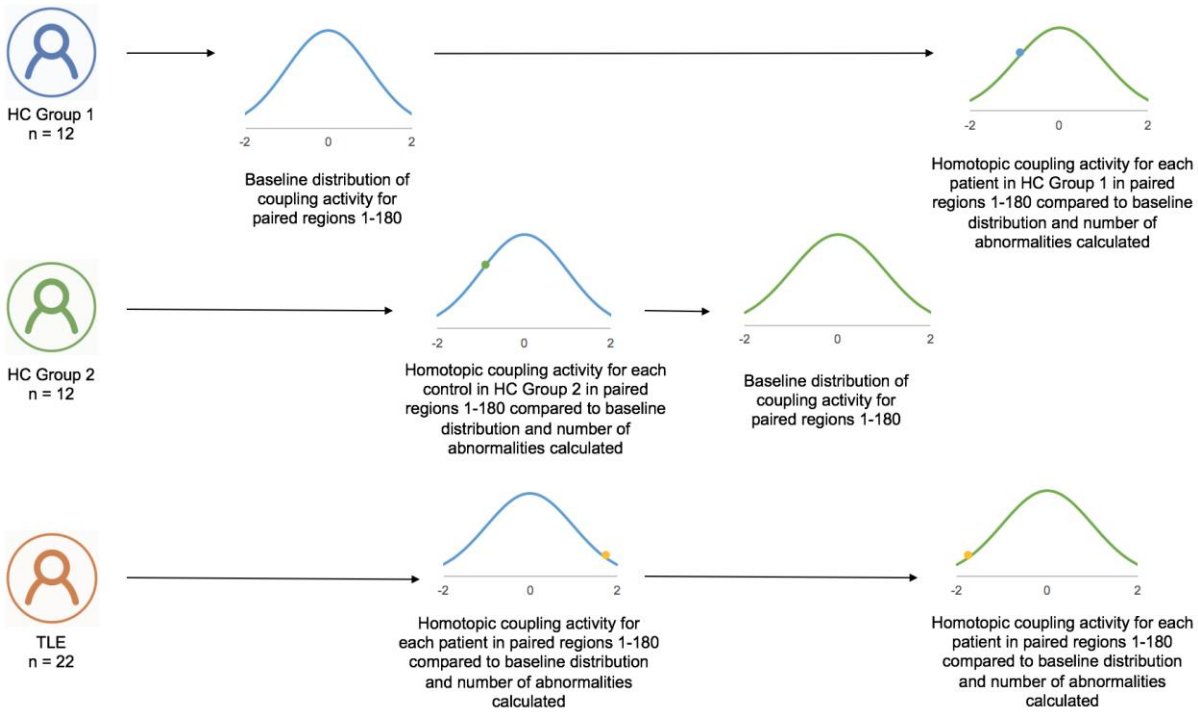

Figure 2-2. *Bootstrapping procedure.* This process was replicated 500 times, with HC randomly assigned to HC Group 1 and HC Group 2 each time. HC = healthy control sample; TLE = temporal lobe epilepsy patient sample.

We were also interested in determining if PWE showed global alterations in homotopic coupling. A global measure of homotopic coupling was obtained for each participant by calculating the mean homotopic coupling value across all 180 regions. A baseline distribution of global homotopic coupling using all controls was created, and global homotopic coupling in PWE were compared to this distribution to identify PWE whose global homotopic coupling activity fell above or below two standard deviations from the mean of this distribution. PWE with global homotopic coupling abnormality were recorded for both resting-state and movie-driven fMRI.

2.9 Regional Distribution of Homotopic Coupling Abnormalities

To determine which regions showed homotopic coupling abnormalities in PWE, the total number of abnormalities in each region were recorded. Given the regional variation that

homotopic coupling shows, the following analyses explore differences in homotopic coupling values and the relationship to cognitive performance between movie-viewing and resting-state, and between PWE and controls in the 22 functionally distinct sections demarcated by the Glasser parcellation (Glasser et al., 2016). The application of larger parcellations for the following analyses allows us to determine how homotopic coupling changes throughout the cortex while reducing the number of comparisons that we perform. The average homotopic coupling value for each of the 22 sections in PWE and controls in movie and rest were calculated. Mean homotopic coupling values in each of the 22 sections were evaluated using a 2x2 mixed analysis of variance (ANOVA) in SPSS to determine the role of scan type (movie vs rest) and group (patient vs control) in each section.

2.10 Neuropsychological Performance and Homotopic Coupling

To evaluate the relationship between homotopic functional coupling and cognition, the average coupling value for each section in PWE and controls was correlated with all available neuropsychological scores and scores on the movie-memory test. To account for multiple comparisons, a false discovery rate (FDR) correction was applied at a threshold of $p < 0.05$ (Benjamini & Hochberg, 1995). This procedure ranks the p-values of all comparisons in ascending order, and the adjusted p-value is equal to a test's rank (i) divided by the total number of tests (N) and multiplied by the significance threshold (D), 0.05. Comparisons whose p-values are equal or than the adjusted D-level are significant. Next, to evaluate the relationship between high and low homotopic functional coupling and cognition, a median split was performed on the patient's average coupling value for each section. This process identified PWE with high and low connectivity, and scores on the movie-memory test and neuropsychological results were compared between these two patient groups for each of the 22 sections in both movie and resting-state. To understand this relationship in a group of neurologically healthy adults, this process was repeated for controls in both resting state and movie. Finally, to determine the extent to which homotopic coupling is task specific, difference scores were calculated between mean homotopic coupling values in each section between movie and resting state, in both movies and controls. Next, difference scores for PWE and controls were correlated with the corresponding

sample's neuropsychological and movie-memory test scores. To account for multiple comparisons, a false discovery rate (FDR) correction was also applied at a threshold of $p < 0.05$ (Benjamini & Hochberg, 1995).

Chapter 3

Results

3.1 Homotopic Coupling Abnormalities

A baseline distribution of coupling activity for each of the 180 regions of the Glasser parcellation were established from the control sample. The homotopic coupling value for each PWE in each region was compared to the corresponding baseline distribution and abnormal values were identified as those above or below two standard deviations from the mean. These comparisons revealed that all PWE showed unique distributions of abnormal homotopic functional coupling during movie-viewing and resting-state scans, ranging from 5 to 63 regions affected per patient during movie-viewing and 4 to 52 regions during resting-state. (Figure 3-1).

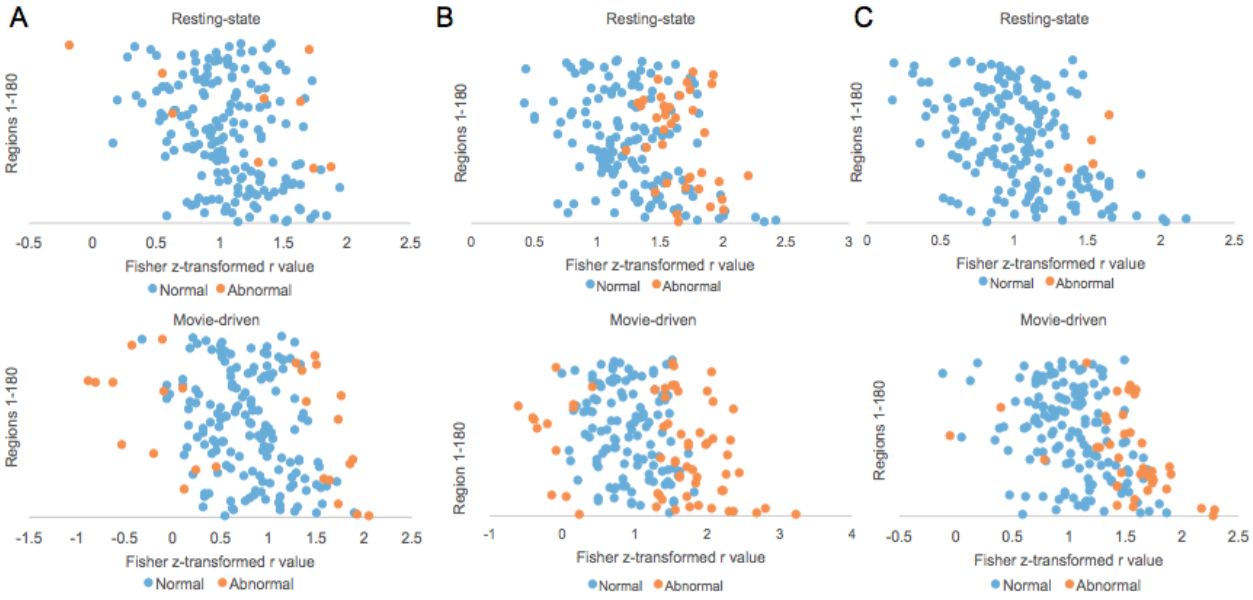

Table 3-1. *Patient specific Homotopic Coupling Abnormalities.* Fisher-transformed correlation coefficients (Z-values) between all 180 regions during movie-viewing and resting-state in A) 27-year-old Black male, duration of epilepsy = 26 years; B) 21-year-old White male, duration of epilepsy = 2 years; C) 21-year-old White female, duration of epilepsy = 12 years. Blue dots represent Z-values that fall within 2 SD of the mean homotopic coupling value of controls in each respective region, and orange dots represent Z-values that fall outside 2 SD of the mean.

The number of homotopic functional coupling abnormalities, identified by the bootstrapping procedure using half of the control sample to create the baseline distribution of coupling activity for all 180 regions, were identified in PWE and controls. Using a 2x2 mixed model analysis of variance (ANOVA), the influence of scan type (rest v. movie) and group (PWE v. controls) on the number of identified homotopic functional coupling abnormalities was investigated. This revealed a significant main effect of group due to a greater number of homotopic functional coupling abnormalities in the PWE sample, $F(1,44) = 8.50$, $p = .006$, $\eta^2 = .19$. Neither a main effect of scan ($p = .128$) nor a significant interaction between scan type and group ($p = .390$) were observed. An analysis of the simple effects revealed that PWE do not show significantly more abnormalities than controls either while watching the movie, $p = .06$, or during resting-state, $p = .08$. The extra power afforded by combining the two simple effects into a main effect is required for differentiation between PWE and controls. These results are displayed graphically in Figure 3-2.

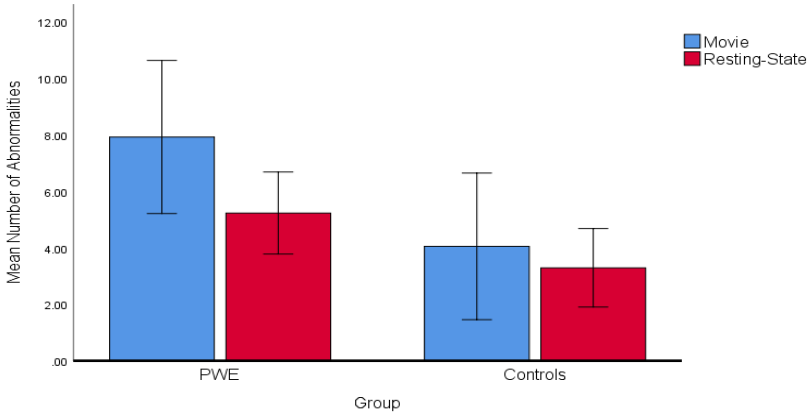

Figure 3-2. *Homotopic Coupling Abnormalities.* Results of a 2x2 mixed ANOVA reveal a significant main effect of group such that PWE display a greater number of abnormalities than the control sample. Error bars represent 95% confidence intervals.

PWE showing global alterations in homotopic coupling, where their mean homotopic functional coupling value was above or below two standard deviations in the baseline distribution of global homotopic connectivity using the control sample, were identified in the

resting-state and movie-viewing paradigms. Five PWE showed global alterations in homotopic functional coupling during resting-state, with four showing increased activity compared to controls and one showing decreased activity compared to controls. Four PWE showed global alterations in homotopic functional coupling in the movie-viewing paradigm, with three showing increased overall activity compared to controls, and one showing decreased activity overall.

3.2 Regional Distribution of Homotopic Coupling Abnormalities

Regional variation in homotopic coupling abnormalities in the PWE sample was observed, with abnormal connectivity values existing within and outside of the temporal lobe. The number of homotopic functional coupling abnormalities in the 180 regions of the Glasser parcellation ranged from 0-8 in movie-viewing, with the greatest number of abnormalities identified in regions in the dorsal stream, middle temporal (MT+) complex, premotor cortex, and the superior parietal and intraparietal sulcus (IPS) cortex (M = 2.96, SD = 1.85). The number of homotopic functional coupling abnormalities ranged from 0-9 in resting-state (M = 2.57, SD = 1.72) with the greatest number of abnormalities identified in regions in the ventral stream, premotor cortex, and the posterior cingulate cortex. The number of functional coupling abnormalities per region in movie-viewing and resting-state are plotted in Figure 3-3.

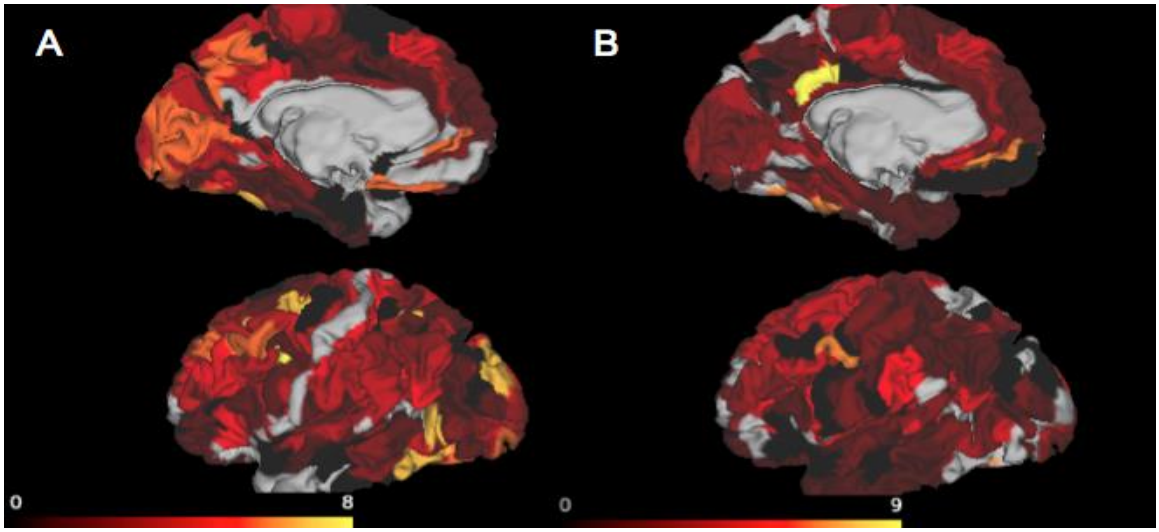

Figure 3-3. *Number of Homotopic Coupling Abnormalities per Region in PWE*. Homotopic coupling abnormalities per region in PWE (n = 22) during movie-viewing (A) and resting-state (B). The grey cortex represents regions where no PWE showed abnormalities.

Given that homotopic coupling activity shows regional variation in PWE and controls during both resting-state and movie-viewing (see Figure 3-4), a 2x2 mixed model ANOVA was used to investigate the role of scan type and group on changes in homotopic coupling activity in each of the 22 functionally distinct sections of the Glasser parcellation. To account for the multiple comparisons required of this analysis, a FDR correction at a threshold of $p < 0.05$ was applied, with 66 comparisons performed (Benjamini & Hochberg, 1995). The results of this analysis are summarized in Appendix D.

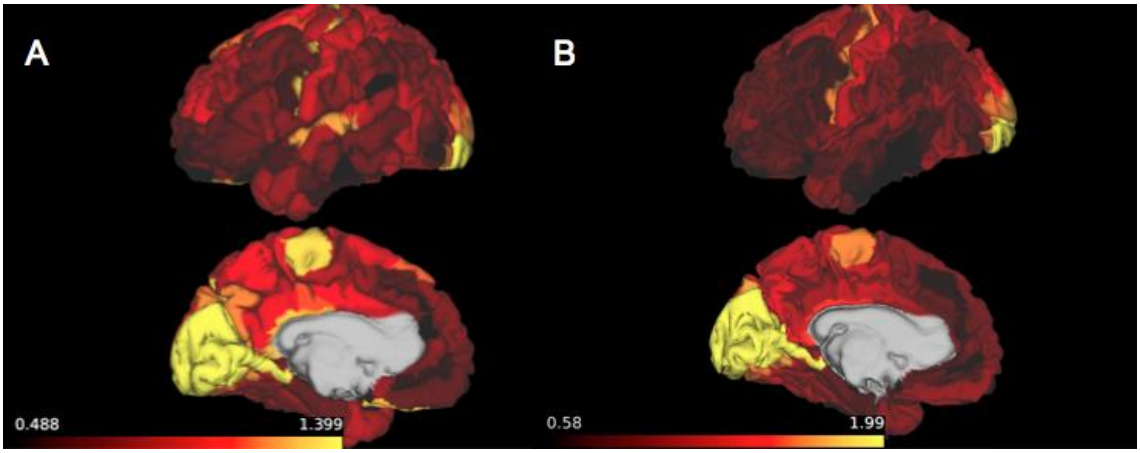

Figure 3-4. *Average Regional Homotopic Coupling Activity in Controls.* Average regional homotopic coupling activity for the control sample (n = 24) in movie-viewing (A) and resting-state (B). Activity is represented by Fisher-transformed correlation coefficients (Z-values).

A significant main effect of scan was found in 13 sections, and of these, homotopic functional coupling was significantly higher at rest than in the movie-viewing paradigm. These regions include V1, the early visual cortex, the dorsal and ventral stream, MT+ cortex, the early somatosensory and motor cortex, the sensori-motor associated paracentral lobular and mid cingulate cortex, the insular and frontal opercular cortex, the medial temporal cortex, the sensory "bridge" regions of the temporal-parietal-occipital junction, the superior parietal and IPS cortex, the inferior parietal cortex, and the posterior cingulate cortex (Figure 3-5).

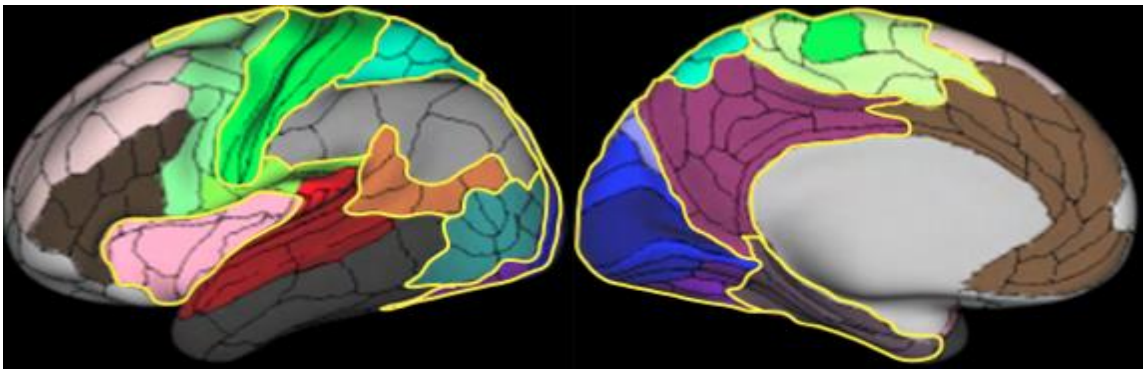

Figure 3-5. *Sections Displaying Higher Resting-State Homotopic Coupling.* Outlined sections of the Glasser parcellation showing higher resting-state homotopic coupling than movie-viewing (Glasser et al., 2016).

A significant interaction between scan type and group was observed in early auditory cortex, $F(1,42) = 7.83$, p-FDR = .038, $\eta^2 = .19$. Looking to the simple effects, homotopic coupling activity between PWE and controls in the early auditory cortex do not differ in movie-viewing (p = .413). However, activity in this region between PWE and controls does differ in resting-state, with PWE displayed higher homotopic coupling activity than controls, $T(1,42) = 2.78$, p =.008. These results are displayed graphically in Figure 3-6.

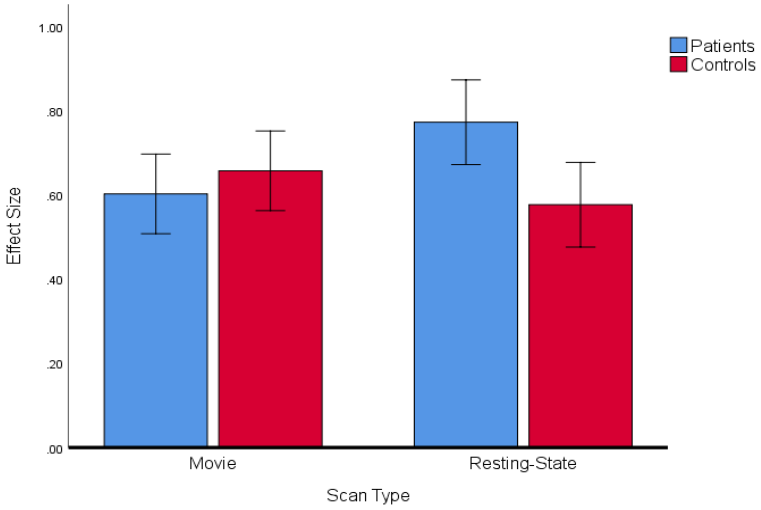

Figure 3-6. *Homotopic Coupling in the Early Auditory Cortex.* Results of a 2x2 mixed ANOVA reveal a significant interaction, suggesting that the group differences depend on scan type. Effect size is measured as the mean Fisher-transformed correlation coefficients (Z-values). Error bars represent 95% confidence intervals.

3.3 Neuropsychological Performance and Homotopic Coupling

Pearson correlation coefficients between homotopic functional coupling in each of the 22 sections and standardized neuropsychological scores and scores on the movie-memory test were calculated, for resting-state and movie-viewing data, for PWE and healthy controls. 440 correlations were performed in the control sample, encompassing the relationship between 10 neuropsychological test scores and homotopic coupling activity in 22 sections of the Glasser parcellation within two scanning paradigms. 124 correlations were performed in the PWE sample, encompassing the relationship between 71 neuropsychological test scores and homotopic coupling activity in 22 sections within two scanning paradigms. Correlations were performed in each sample between coupling activity and neuropsychological performance in each of the 22 sections independently, for both resting-state and movie-viewing scans. Notably, PWE have additional neuropsychological assessment results from evaluations performed during their stay in the Adult Epilepsy Service. To account for the multiple comparisons required of this analysis, a FDR correction at a threshold of $p < 0.05$ was applied (Benjamini & Hochberg, 1995). FDR correction was performed in the same way as the correlational analysis, resulting in 71 comparisons for PWE and 10 for controls for each section within each scan. In PWE, 8 correlations survived the FDR correction, and 2 correlations survived the FDR correction in the control sample, all in the resting-state paradigm.

In PWE, homotopic functional coupling in V1 at rest was found to be correlated with the Verbal Paired Associates (VPA) delayed raw and scaled scores (from the Wechsler Memory Scale-Fourth Edition, WMS-IV; Wechsler, 2009), the VPA percent retention scaled scores, Faces immediate memory raw scores (from the Wechsler Memory Scale-III, WMS-III; Wechsler, 2009), raw copy scores from The Rey Complex Figure Test (RCFT; Strauss, Sherman, & Spreen, 2006), time 1 raw scores from the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), Performance Intelligence Quotient Scores (PIQ), and Full Scale Intelligence Quotient Scores (FSIQ), from the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI II; Wechsler, 2011), or from the WAIS-IV (Wechsler, 2008). In controls, homotopic functional coupling in the inferior parietal cortex at rest was found to be significantly correlated with total number of errors and trials to criterion on the CALT. We computed 95% confidence intervals (CI) for the difference between the correlations, where an interval that includes 0

suggests a nonsignificant difference (Zou, 2007). The difference between the correlation between CALT errors and homotopic coupling in the inferior parietal cortex at rest were not found to differ significantly between PWE and controls, 95% CI: [0.00, 0.63]. The difference between the correlation between CALT trials and homotopic coupling in the inferior parietal cortex at rest was found to differ significantly between PWE and controls, 95% CI: [-0.13, 0.59]. These results are summarized in Table 3-1 and displayed graphically in Figures 3-7 and 3-8. For homotopic coupling activity derived during movie-viewing, no correlations with any of the neuropsychological measures or movie memory test, in any of the 22 sections, survived the FDR correction in PWE or controls.

Table 3-1

Relationship between Resting-State Homotopic Coupling Activity and Neuropsychological Performance in PWE and Controls

Scan	Region	Sample	Assessment Score Type	*n*	*r*	*p*-FDR
Resting-state	V1	PWE	VPA delayed raw	20	.70	.036*
			VPA delayed scaled	20	.60	.044*
			VPA percent retention scaled	17	.66	.041*
			Faces immediate memory raw	17	.67	.036*
			RCFT raw copy	17	.69	.036*
			BNT time 1 raw	17	.67	.038*
			PIQ	19	.68	.037*
			FSIQ	19	.65	.039*
Resting-state	Inferior Parietal Cortex	Healthy Controls	CALT errors	23	-.72	.000**
			CALT trials to criterion	23	-.71	.000**

Note. Significant Fisher-transformed Pearson correlations.
* significant at the .05 level
** significant at the .001 level

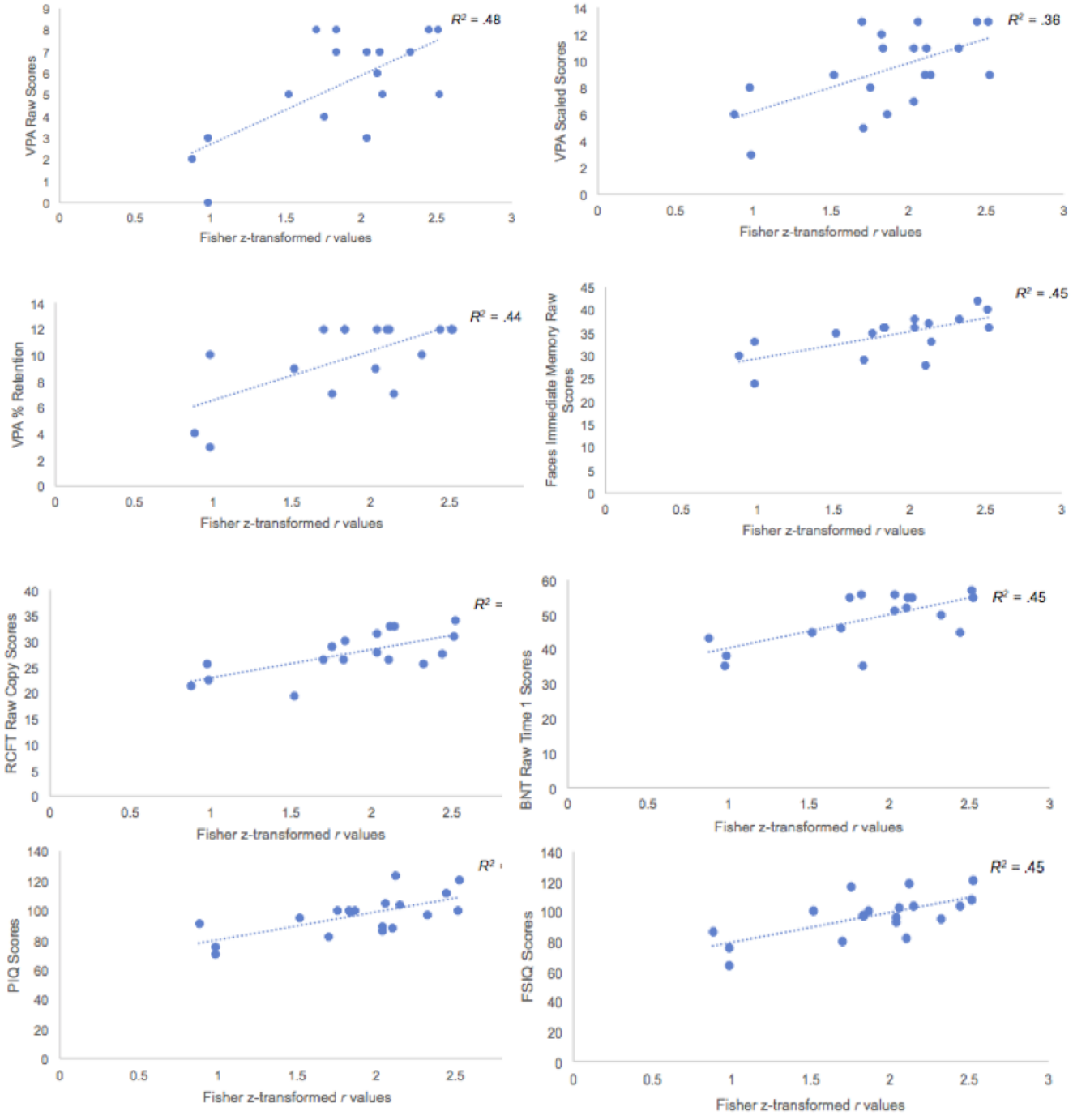

Figure 3-7. *Relationship between Resting-State Homotopic Coupling Activity in V1 and Neuropsychological Performance in PWE.* Significant Fisher-transformed Pearson correlations.

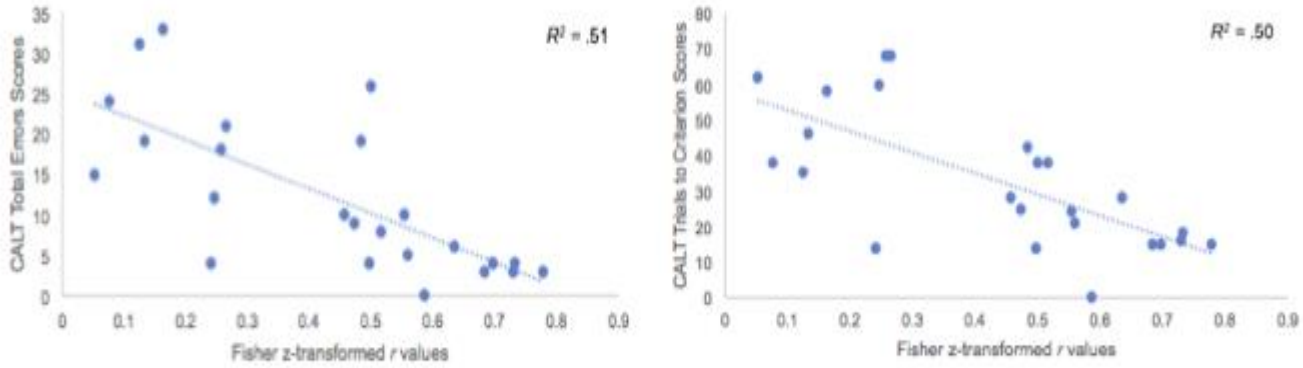

Figure 3-8. *Relationship between Resting-State Homotopic Coupling Activity in the Inferior Parietal Cortex and Neuropsychological Performance in Controls.* Significant Fisher-transformed Pearson correlations.

In each of the 22 sections, a median split was performed separating those with high homotopic coupling activity from those with low homotopic coupling activity. This was done separately for PWE and controls, for coupling based on movie-viewing and resting-state data. Neuropsychological test scores were then compared between subgroups with high and low coupling values. To control false-positive rate given the multiple comparisons performed, a FDR correction at a threshold of $p < 0.05$ was applied (Benjamini & Hochberg, 1995). FDR correction was performed separately for PWE and controls within each section for the movie and resting-state paradigms, resulting in 71 comparisons for PWE and 10 comparisons for controls for each section within each scan. The significant results of the independent-samples t-tests conducted on neuropsychological scores between high and low homotopic functional coupling groups are summarized in Table 3-2.

For coupling derived from the movie-viewing paradigm, a significant difference was found in four scores from the RVDLT between controls with low and high homotopic functional coupling activity in the superior parietal and IPS cortex. These include RVDLT trials four and five, and the total and delayed scores of the RVDLT. In the posterior cingulate cortex during movie-viewing, a significant difference was found in five scores from the RVDLT between controls with low and high homotopic functional coupling. These include RVDLT trials two and three, total, delayed, and true positive scores of the RVDLT. In the inferior parietal cortex during resting state, a significant difference was found in the total number of errors and trials to completion scores on the CALT between control participants with low and high homotopic

functional coupling activity in this region. In PWE, no differences in neuropsychological scores, in any region between groups exhibiting high and low coupling, were found to survive FDR correction in movie-viewing or resting-state.

Table 3-2

Results from independent-sample t-tests highlight a significant difference in scores on neuropsychological assessments between controls with high and low homotopic functional coupling.

Scan Type	Region	Test	Mean	Standard Deviation	T	Df	Sig. (two tailed) FDR
Movie	Superior parietal and IPS cortex	RVDLT Time 4	High: 12.83 Low: 9.66	1.59 2.23	-4.01	22	0.03*
		RVDLT Time 5	High: 13.25 Low: 10.17	2.01 2.52	-3.32	22	.038*
		RVDLT Total	High: 54.42 Low: 41.117	10.71 10.56	-3.05	22	.038*
		RVDLT Delay	High: 13.25 Low: 10.42	2.00 2.47	-3.09	22	.038*
Movie	Posterior cingulate cortex	RVDLT Time 2	High: 10.12 Low: 6.58	2.82 1.88	-3.659	22	.008*
		RVDLT Time 3	High: 12.08 Low: 9.00	2.50 3.05	-2.710	22	.046*
		RVDLT Total	High: 54.33 Low: 41.25	11.04 10.32	-2.99	22	.044*
		RVDLT Delay	High: 13.17 Low: 10.50	1.85 2.67	-2.836	22	.046*
		RVDLT False Positives	High: .250 Low: 1.45	.45 1.29	3.036	21	.046*
Rest	Inferior parietal cortex	CALT errors	High: 6.91 Low: 17.92	6.71 8.67	3.38	21	.033*
		CALT Trials	High: 22 Low: 45.33	9.03 17.96	3.87	21	.033*

Note. Significant Fisher-transformed Pearson correlations.
* significant at the .05 level
** significant at the .001 level

We wanted to explore whether regional changes in coupling activity between movie and resting-state scans in PWE and controls showed a relationship with cognitive performance to determine the extent to which homotopic coupling in a given region is task-specific. Difference scores were calculated for each of the 22 sections and 220 Pearson correlations were performed within the control sample, and 1562 correlations were performed within the PWE sample. To control false-positive rate given the multiple comparisons performed, a FDR correction at a threshold of $p < 0.05$ was applied (Benjamini & Hochberg, 1995). FDR correction was performed separately for PWE and controls within each section, resulting in 71 comparisons for

PWE and 10 comparisons for controls for each of the 22 sections of the Glasser parcellation. Three significant FDR-corrected Pearson correlations were found between difference scores and standardized neuropsychological scores and movie-memory test scores in PWE and controls. These results are plotted in Figures 3-9 and 3-10. In controls, a significant correlation was found between difference scores in homotopic functional coupling between movie-viewing and resting-state in the inferior parietal cortex and total number of trials to criterion on the CALT (r = -.73, p-FDR = .000). In PWE, two significant correlations were found between differences scores in the premotor cortex and standardized neuropsychological scores. These include CALT trials to criterion (r = -.66, p-FDR = .036) and VPA percent retention scaled scores (r = .67, p-FDR = .047).

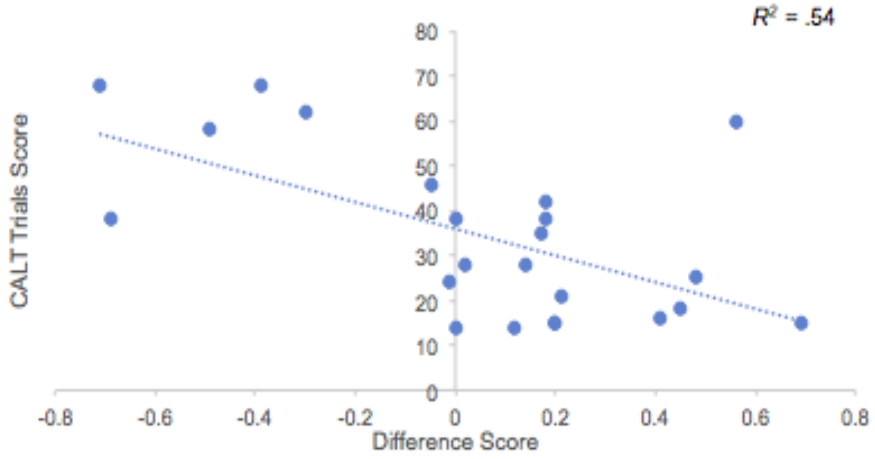

Figure 3-9. *Relationship between Difference Scores in Homotopic Coupling Activity in the Inferior Parietal Cortex and Neuropsychological Performance in Controls***.** FDR-corrected Pearson correlation in controls between difference scores in homotopic functional coupling between movie-viewing and resting-state in the inferior parietal cortex and total number of trials to criterion on the CALT.

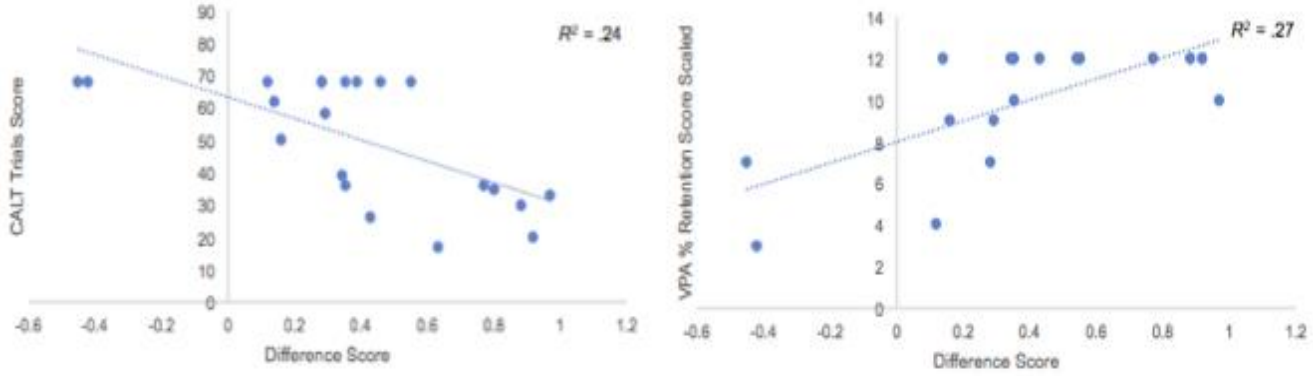

Figure 3-10. *Relationship between Difference Scores in Homotopic Coupling Activity in the Premotor Cortex and Neuropsychological Performance in PWE***.** FDR-corrected Pearson correlation in PWE between difference scores in homotopic functional coupling between movie-viewing and resting-state in the premotor cortex and total number of trials to criterion on the CALT and VPA percent retention scaled scores.

Chapter 4

Discussion

4.1 Major Findings

We demonstrate the utility of resting-state and movie-driven fMRI for detecting homotopic functional coupling abnormalities in persons with refractory TLE. Whereas homotopic coupling has been consistently observed at rest in neurotypical populations (Bernasconi et al., 2010; Tzourio-Mazoyer et al., 2018; Mancuso et al., 2019) and PWE (Ji et al., 2014; Yang et al., 2014; Xu et al., 2014), our findings show that assessing functional networks using naturalistic stimulation provides supplementary data about the epileptic network during cognitive engagement. Specifically, homotopic coupling activity in the inferior parietal and early auditory cortices highlights group differences specific to movie-viewing and resting-state scanning. In addition, we show evidence of whole-brain abnormal homotopic coupling in PWE, which lends support to the idea that people with focal epilepsy have widespread, network-level, brain abnormalities that are not restricted to the EZ. These widespread abnormalities may be indicative of neural reorganization in response to pathological epileptic activity. Finally, we show that the relationship between homotopic coupling at rest, and performance on neuropsychological assessments, differs between groups and is more robust than that of movie-driven fMRI, potentially due to reduced homotopic coupling during naturalistic stimulation. This may be a result of higher order cognitive functions being generally more lateralized compared to resting state activity (Mancuso et al., 2019).

4.2 Homotopic Coupling Abnormalities

In both resting-state and movie-driven fMRI, PWE exhibited significantly more abnormal homotopic coupling than healthy controls, which supports our hypothesis that functional connectivity between homologous regions is altered in response to the generation of epileptic activity throughout the brain. These results are reflective of findings of altered interhemispheric

connectivity between temporal regions in mTLE identified using resting-state fMRI (Xu et al., 2014). In these PWE, larger connectivity differences were associated with recurrent seizures after surgery (Xu et al., 2014). Pizoli et al., (2011) report the normalization of interhemispheric functional connectivity in a child with epilepsy following a corpus callosotomy, further substantiating the idea that homotopic coupling is a potentially sensitive indicator of healthy neurological functioning. Moreover, these findings parallel patterns of altered homotopic coupling established using resting-state and task-based fMRI in individuals with neurological conditions such as Alzheimer's disease (Wang et al., 2015), as well as in autism (Anderson et al., 2011), schizophrenia (Hoptman et al., 2012), and cocaine addiction (Kelly et al., 2011). Our results contribute to the existing literature documenting abnormal intrahemispheric connectivity (Lee et al., 2014; McCormick et al., 2014) and interhemispheric connectivity (Ji et al., 2014) in PWE by demonstrating that homotopic coupling, a fundamental feature of the brain's structural and functional architecture, is altered among persons with refractory TLE. Importantly, we demonstrate the enduring nature of homotopic coupling abnormalities through their identification in PWE at rest and while watching a suspenseful and engaging audiovisual film clip.

All PWE in our sample (n = 22) exhibited abnormalities in homotopic coupling, ranging from 5 to 63 regions affected per patient during movie viewing and 4 to 52 regions during resting state. The dissimilarity in the degree and location of altered connectivity between homologous regions identified between PWE as well as in a single patient between rest and movie-viewing scans suggests that homotopic coupling changes in epilepsy can be patient-specific. Patient-specific alterations in functional connectivity in PWE have also been demonstrated in cortical regions found to be correlated with the seizure onset zone using iEEG (Marino et al., 2019). Furthermore, using resting-state fMRI, Neal et al., (2020) mapped patient-specific epilepsy networks and showed that greater surgical disconnection of implicated regions was associated with an increase in neuropsychological performance on measures of working memory and language. In addition, we found that nine PWE in our sample showed global, non-localized homotopic coupling alterations in either resting-state or movie-driven fMRI. This finding reflects literature that describes widespread functional connectivity alterations in addition to localized changes (Liao et al., 2010; McCormick et al., 2014). It is possible that extensive alterations in homotopic coupling may reflect large-scale neural reorganization in TLE. Interestingly, four PWE only manifested abnormalities during rest, while three PWE only manifested abnormalities

during movie-viewing, and only one exhibited global alterations in homotopic coupling in **both** resting-state and movie-viewing paradigms. This further demonstrates that homotopic coupling can manifest differently during rest and while watching an engaging film, and thus, having a multimodal functional imaging approach to evaluate neural changes in epilepsy can be beneficial.

4.3 Regional Distribution of Homotopic Coupling Abnormalities

We observed that homotopic coupling abnormalities in PWE showed compelling regional variation, with abnormal coupling identified at rest and during movie-viewing within and outside the temporal lobe. Critically, the identification of network disruptions in regions beyond the EZ reinforce the perspective of epilepsy as a network disorder. In individuals with mTLE, abnormal connectivity in extratemporal regions has been observed using both photon emission computed tomography (SPECT) and positron emission tomography (PET) (Shulman, 2000). Furthermore, functional alterations in the regions contralateral to the epileptic focus have been identified, suggesting pathological activity in one hemisphere influences homotopic regions (Bettus et al., 2009).

My demonstration that homotopic coupling is abnormal in regions outside the epileptogenic focus suggests that epileptic activity can exert distant effects on neural integrity and influence interhemispheric connectivity. Such abnormalities provides a persuasive explanation for the continuation of seizure activity in up to 30% of PWE after resectional surgery, as well as the widespread and heterogeneous cognitive and neurobehavioural changes that are seen in TLE (Haneef et al., 2015). Diffuse changes in functional connectivity in focal epilepsies may occur through seizure generalization, or secondary epileptogenesis, in which a single well-connected neural circuit distributes pathological neural changes across the cortex (Doucet et al., 2013). Therefore, a comprehensive whole-brain approach to evaluating neural changes in epilepsy is imperative in the presurgical assessment of individuals with TLE.

Our findings extend observations of abnormal functional connectivity outside the EZ using resting-state fMRI, by employing a perceptually rich and engaging film clip. During movie-viewing, regions in the dorsal stream, MT+ complex, premotor cortex and the superior parietal and IPS cortex displayed the greatest number of homotopic coupling abnormalities in

PWE. During resting-state, significant abnormalities were identified in regions in the ventral stream, premotor cortex, and the posterior cingulate cortex. Variation in the location of homotopic coupling abnormalities identified by resting-state and movie-driven fMRI demonstrate that these paradigms are differentially sensitive to changes in functional connectivity. This implies that when combined, these functional imaging approaches are even more sensitive to abnormalities in homotopic coupling.

Heterogeneity between scanning paradigms can be interpreted in the context of studies that show homotopic coupling to be dependent on both cortical location and task demands. Using a meta-analytic homotopic connectivity approach, Mancuso et al., (2019) maintain that the strength of homotopic coupling in neurotypical samples shows spatial inhomogeneity for particular functional purposes. Specifically, the least homotopically connected areas are those such as the lateral and dorsomedial prefrontal cortices and temporal lobe regions, which are typically implicated in higher order cognitive functions such as language and memory (Mancuso et al., 2019). In contrast, medial regions and primary cortices, such as the ventral anterior cingulate and cingulate cortex, show strong homotopic coupling (Stark et al., 2008). These differences are hypothesized to occur as a result of faster-conduction callosal fibers between primary cortices that are engaged in bilateral sensory and motor coordination, whereas slower fibers interconnect associative areas, reflective of functional lateralization (Stark et al., 2008). Slower callosal fibers are associated with hemispheric asymmetry because when one hemisphere is more adept in processing particular information, callosal inhibition increases efficiency in that hemisphere. In contrast, stronger callosal fibers are more likely to be present when both hemispheres cooperate to perform information processing (Schulte & Müller-Oehring, 2010). Thus, regional changes in homotopic coupling between movie-viewing and rest are likely reflective of the scanning paradigms that differentially recruit interhemispheric and intrahemispheric processing.

In PWE and healthy controls, thirteen sections displayed higher resting-state homotopic coupling activity than that observed in movie-driven fMRI. These include mainly primary sensory and medial regions, supporting well-documented findings of higher homotopic coupling at rest in these areas (Stark et al., 2008; Mancuso et al., 2019). Interestingly, the medial temporal lobe showed higher homotopic coupling during rest than in movie-viewing, and this is consistent with observations that memory-associated regions display weaker homotopic coupling during

task performance or cognitive engagement (Rämä et al., 2001). We observed that group differences in the early auditory cortex were greater at rest than during movie-viewing, with PWE showing higher homotopic coupling activity than controls during resting-state. This finding is suggestive of atypical interhemispheric recruitment of sensory regions in TLE.

4.4 Neuropsychological Performance and Homotopic Coupling

Cognitive impairment in epilepsy has typically been interpreted in the context of deficits in localized regions, however, evidence suggests that brain-behaviour relationships in epilepsy are likely mediated by abnormalities in functional networks (Tailby et al., 2018). Cognition is supported by the integration of regionally distributed neural activity and as such, neuropsychological assessments should be interpreted within the context of functional imaging paradigms to identify the multiplicity of connections and regions that may support cognition in PWE. In controls, we observed that lower trials to criterion and total number of errors on the Conditional Associative Learning Test (CALT), which is indicative of good visual memory, was associated with increased homotopic coupling at rest between regions in the inferior parietal cortex. This relationship was not significant in PWE, and only the difference in the correlation between CALT trials to criterion and homotopic coupling activity in the inferior parietal cortex was found to differ significantly between PWE and controls. This suggests that homotopic coupling between the inferior parietal cortical regions supports visual memory performance and may be reflective of healthy cognition. The inferior parietal cortex has been shown to be involved with the integration of information from different sensory modalities, and parietal cortices such as the intraparietal sulcus and intra-occipital sulcus have been associated with visual working memory maintenance (Todd & Marois, 2004). The inferior parietal cortex has been identified as a major hub in resting-state fMRI studies, and has been implicated in a diverse range of higher cognitive functions (Igelström & Graziano, 2017). Furthermore, high homotopic coupling in this region at rest is likely reflective of its role in the DMN, particularly since DMN medial regions could be more homotopically connected than executive regions due to their proximity to the median line (Mancuso et al., 2019). Overall, the inferior parietal cortex is involved with recollection of both verb and visuospatial stimuli (Papagno, 2018), and our results

suggest that strengthened homotopic coupling in this area supports performance of visual and spatial memory tasks.

We found that PWE displayed a positive relationship between homotopic coupling activity in V1 at rest and working memory performance, as well as full-scale FSIQ and PIQ scores. Given the evidence that the temporal lobe supports both long-term and working memory processes (Goodrich et al., 2019), the relationship we observed may be reflective of a compensatory strategy in TLE, due to deficits in this localized region. This interpretation has been regularly employed by researchers who find discordant relationships between cognitive function and functional connectivity in individuals with neurological conditions. For example, in individuals with left TLE, increased recruitment of the left frontal lobe has been associated with proficient verbal fluency (Bonelli et al., 2011). Through the engagement of supplementary neural connections, compensatory mechanisms are hypothesized to maintain cognitive functions that would otherwise be compromised by pathological neural activity (Vakharia et al., 2018). For example, Bettus et al., (2009) found increased functional connectivity during resting-state to the contralateral temporal lobe to be correlated with working memory scores. Additionally, researchers have reported increased homotopic coupling in PWE with mild cognitive impairments in posterior regions such as the sensorimotor cortex and occipital gyrus (Wang et al., 2015). These findings that are indicative of functional reorganization in response to pathological epileptic activity in TLE provides persuasive evidence for the relationship between network flexibility and cognition. The cellular and structural changes that accompany prolonged seizure activity have the potential to affect cognitive neural representations and as such, enable PWE to maintain certain cognitive processes.

We did not observe a relationship between homotopic coupling activity during movie-viewing and cognitive performance in either PWE or healthy controls. This further suggests that homotopic coupling may be modulated differently by rest and movie-viewing. For example, using EEG, Bernasconi et al., (2010) found that activity between homotopic posterior Sylvian regions was correlated when participants made inaccurate temporal order judgements in response to auditory stimuli, and activity in these regions was not correlated when participants were accurate. These findings suggest that coupling strength is task-dependent, and specifically that temporal order judgments are facilitated when the two posterior Sylvian regions are working independently. Thus, reduced coupling during cognitive tasks may not reflect unhealthy

connection, but rather shows that homotopic coupling strength fluctuates in response to the demands of the environment and related cognitive processing. During movie-viewing, distinct patterns of activation have been shown to be associated with the functional properties of specific cortical regions (Hasson et al., 2004). Furthermore, this activation has been found to be associated with specific elements of the movie, such as correlated activity around the posterior postcentral gyrus in frames showing delicate hand movements during various motor tasks (Hasson et al., 2004). These findings suggest that the emotional, cognitive and sensory demands of the movie may evoke more functional connectivity between regions and their well-connected hubs rather than coordinated homotopic coupling that has been found to underlie cognition at rest. This interpretation is in line with our findings that showed thirteen regions eliciting higher homotopic coupling activity at rest than during movie-viewing.

During movie-viewing, healthy controls with high and low activity between homotopic regions in the superior parietal and IPS cortex and posterior cingulate cortex displayed differences in visual memory performance, as measured by the RVDLT. Specifically, higher homotopic coupling activity in these regions was associated with better visual memory performance. The posterior cingulate cortex has been implicated in human memory processes, with high cortical activity displayed during autobiographical episodic memory retrieval, as well as with the recognition of familiar words, objects and places (Sugiura et al., 2005; Heun et al., 2006). Our results support these findings, as better performance on the RVDLT requires the recognition of objects shown to participants over five learning trials, and so increased homotopic coupling in this region may facilitate performance on this task. Similarly, the superior parietal and IPS cortex have been shown to be particularly activated during tasks requiring the mental rotation of two-dimensional objects (Alivisatos et al., 1997) and activity in the superior parietal lobule has consistently been found to correlate with working memory task performance (Wager and Smith, 2003).

In PWE, a greater change in coupling activity in the premotor cortex between movie-viewing and resting-state was associated with better visual and verbal memory performance on the Conditional Associative Learning Test and Verbal Paired Associates subtest of the WMS-IV. In this region, higher homotopic coupling activity was observed during resting-state in PWE. Healthy controls did not complete the Verbal Paired Associates subtest, and so we cannot conclude that this observation is characteristic of PWE with focal epilepsy. However, the

relationship between differences scores in regions in the premotor cortex and performance on the Conditional Associative Learning Test was not observed in healthy controls, which suggests that the task specificity of homotopic coupling in this region is related to epileptic activity in TLE. These findings demonstrate that the change between homotopic coupling activity in a particular region is related to cognition in ways specific to the healthy control and PWE samples. Specifically, a greater difference in coupling activity between scanning paradigms is associated with better visual and verbal memory performance.

4.5 Limitations

While highlighting abnormalities in homotopic coupling in PWE, our results do not provide directional explanations and this limits our power to infer whether altered connectivity between homologous regions is driven by the lesioned or contralateral hemisphere. Our patient sample showed heterogeneous pathology, age of onset, handedness, presence of mesial temporal sclerosis, and presumed seizure laterality. However, we were limited in our small PWE sample size of 22 to explore within-group differences in homotopic coupling relative to duration of illness, as demonstrated by Yang et al., (2014). Furthermore, homotopic connectivity has been shown to be influenced by handedness, specifically, it has been shown that the degree to which language is left lateralized, which is related to handedness, is inversely related to the degree to which left frontal regions drive activity in homotopic right frontal regions (Seghier et al., 2011). It is possible that our findings in PWE are confounded by the use of antiepileptic drugs, which can alter connectivity and produce cognitive impairment (Ji et al., 2014). Finally, there are important limitations to consider when applying a functionally informed parcellation scheme, such as the Glasser parcellation. As there is evidence of neural reorganization and alteration of functional connectivity in PWE (Barnett et al., 2017), patient specific variability could mean that the functional consistency of the regions in the patient group are less reliable than in the control sample, particularly in higher-order cortical regions. \

4.6 Conclusions

We assessed changes in homotopic coupling and the relationship between such activity and performance on standardized neuropsychological assessments among persons with refractory TLE and healthy controls during movie-viewing and resting-state fMRI paradigms. This research demonstrates measurable differences in interhemispheric connectivity found in PWE compared to controls in both movie-viewing and resting-state fMRI paradigms. PWE displayed patient-specific regional patterns of homotopic coupling abnormalities that were both paradigm and patient specific. This suggests that homotopic coupling is affected by the manifestation of epilepsy via seizure propagation or neuropsychological manifestations of the disorder.

Homotopic coupling abnormalities were widespread across cortical regions as well as within the temporal lobe, which highlights the remote neural effects of focal epilepsies. Furthermore, we observed a relationship between homotopic coupling at rest and visual memory performance in healthy controls in the inferior parietal cortex, and in PWE in V1. Investigating the relationship of the epileptic network to cognition requires more attention as discordant findings in the field may be reflective of patient-specific functional reorganization or pathological network activity. However, our findings show that networks beyond those considered canonical to memory processes in the healthy brain must be evaluated in persons with TLE.

We report evidence of alterations in functional connectivity in PWE identifiable in a naturalistic stimulation paradigm, demonstrating the utility of movie-driven fMRI to investigate network integrity in epilepsy. Variability in findings between resting-state and movie-driven fMRI demonstrate that there are inherent advantages to the combined use of complex natural stimulation and resting-state fMRI to discover the underlying functions of different brain regions. Movie-driven fMRI is able to identify alterations in functional networks that support engaged cognition, while resting-state fMRI is able to identify abnormal networks that are critical for the maintenance of healthy cognitive functioning. Furthermore, we demonstrate that the identification of alterations between homotopic regions and how homotopic coupling relates to cognition is dependent on the demands of the scanning environment. Evaluating both resting-state and movie-driven fMRI activated networks may provide greater insight into the functional

capacity of neural homotopic systems, beyond what is activated by a task-specific paradigm. Our findings indicate that TLE may promote the reorganization of networks supporting cognitive functions such as memory and indicate that the consideration of both resting and naturalistically stimulated connectivity may be important for informing the presurgical assessment of persons with refractory TLE.

4.7 Future Directions

By engaging simultaneous neurocognitive networks, movie-driven fMRI provides the opportunity to assess auditory and visual processing, emotion processing, social cognition and memory. We have demonstrated that this paradigm, as well as resting-state fMRI, is sensitive to changes in homotopic coupling in PWE, and we anticipate that these paradigms will be useful for studying the many facets of cognitive and neural changes that accompany epilepsy. A better understanding of the interhemispheric relationships in refractory epileptic networks is crucial, especially those outside the EZ. Our findings demonstrate that those areas least expected can be important for memory and cognition in PWE and a multimodal imaging approach may provide more information than any single technique. Nevertheless, the application of functional connectivity for diagnostic aims requires further validation and follow-up investigations before it can be applied to the clinical management of individual PWE.

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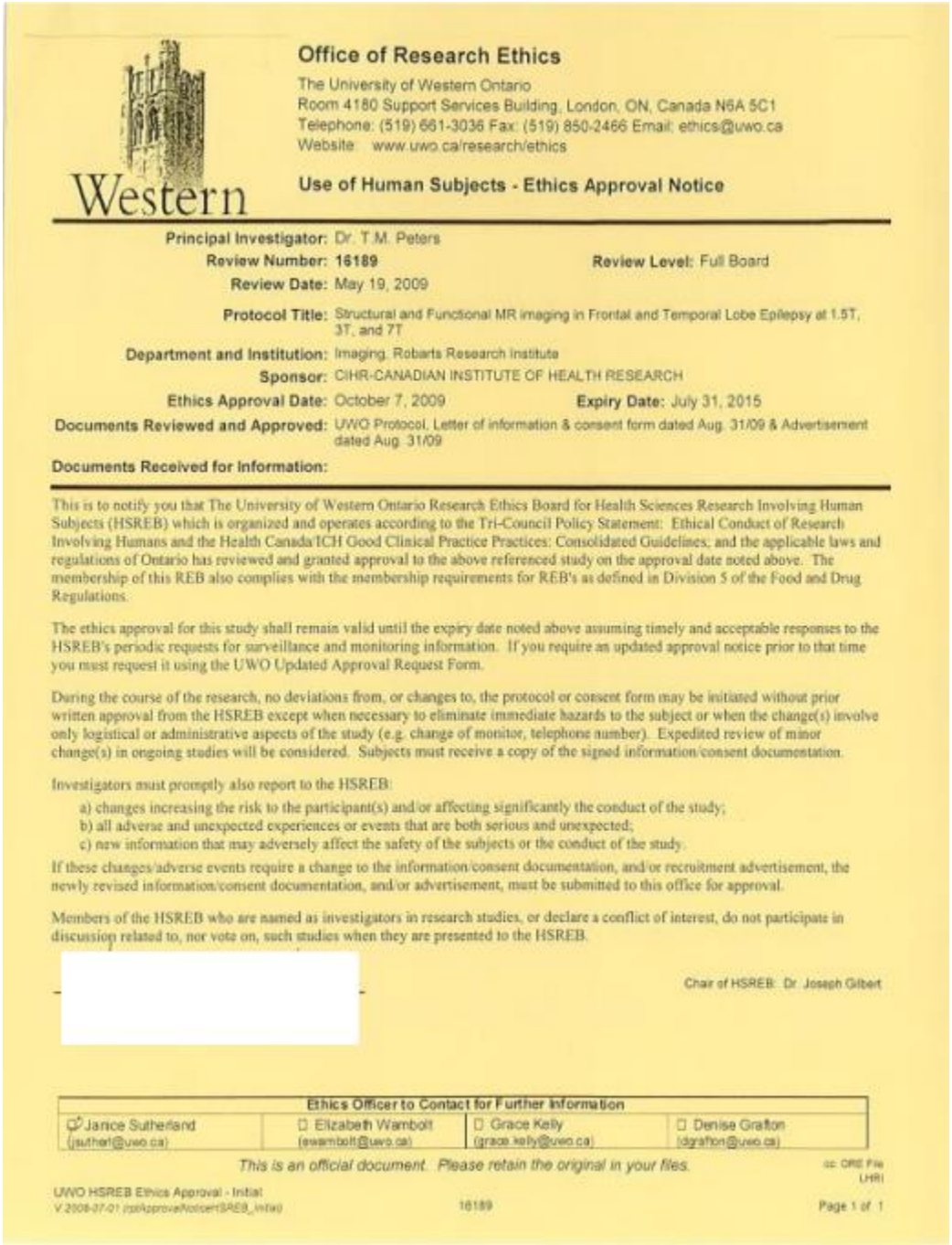
Appendices

Appendix A: Ethical Approval from the Health Sciences Research Ethics Board of the University of Western Ontario



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Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. T.M. Peters
Review Number: 16189 **Review Level:** Full Board
Review Date: May 19, 2009
Protocol Title: Structural and Functional MR imaging in Frontal and Temporal Lobe Epilepsy at 1.5T, 3T, and 7T
Department and Institution: Imaging, Robarts Research Institute
Sponsor: CIHR-CANADIAN INSTITUTE OF HEALTH RESEARCH
Ethics Approval Date: October 7, 2009 **Expiry Date:** July 31, 2015
Documents Reviewed and Approved: UWO Protocol, Letter of information & consent form dated Aug. 31/09 & Advertisement dated Aug. 31/09
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. Joseph Gilbert

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Appendix B: Anatomical and Functional Imaging and Data Preprocessing

Anatomical data preprocessing

The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al., 2010), distributed with ANTs 2.2.0 (Avants et al., 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as the target template. Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847, Dale et al., 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al., 2017). Spatial normalization to the *ICBM 152 Nonlinear Asymmetrical template version 2009c* (Fonov et al., 2009, RRID:SCR_008796) was performed through nonlinear registration with antsRegistration (ANTs 2.2.0), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, RRID:SCR_002823, Zhang et al., 2001).

Functional data preprocessing

For each of the 2 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. A deformation field to correct for susceptibility distortions was estimated based on a field map that was co-registered to the BOLD reference, using a custom workflow of *fMRIPrep* derived from D. Greve's epidewarp.fsl script and further improvements of HCP Pipelines (Glasser et al., 2013). Based on the estimated susceptibility distortion, an unwarped BOLD reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve & Fischl, 2009). Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9, Jenkinson

et al. 2002). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 (Cox & Hyde 1997, RRID:SCR_005927). The BOLD time-series were resampled to surfaces on the following spaces: *fsaverage5*. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Automatic removal of motion artifacts using independent component analysis (ICA-AROMA, Pruim et al., 2015) was performed on the *preprocessed BOLD on MNI space* time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Corresponding "non-aggresively" denoised runs were produced after such smoothing. Additionally, the "aggressive" noise-regressors were collected and placed in the corresponding confounds file. The BOLD time-series were resampled to MNI152NLin2009cAsym standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al., 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, Behzadi et al., 2007). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). Six tCompCor components are then calculated from the top 5% variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, six components are calculated within the intersection of the aforementioned mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. All resamplings can be

performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and template spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

Appendix C: Glasser Parcellation Sections with Corresponding Regions

Table A-1

Glasser Parcellation Sections and Region Names

Section	Region Name	Region Description
1 V1	V1	Primary Visual Cortex
2 Early Visual Cortex	V2	Second Visual Area
	V3	Third Visual Area
	V4	Fourth Visual Area
3 Dorsal Stream	V6	Sixth Visual Area
	V3A	Area V3A
	V7	Seventh Visual Area
	IPS1	IntraParietal Sulcus Area 1
	V38	Area V38
	V6A	Area V6A
4 Ventral Stream	V8	Eighth Visual Area
	FFC	Fusiform Face Complex
	PIT	Posterior InferoTemporal Complex
	VMV1	VentroMedial Visual Area 1
	VMV3	VentroMedial Visual Area 3
	VMV2	VentroMedial Visual Area 2
	VVC	Ventral Visual Complex
5 MT+ Complex	MST	Medial Superior Temporal Area
	LO1	Area Lateral Occipital 1
	LO2	Area Lateral Occipital 2
	MT	Middle Temporal Area
	PH	Area PH
	V4t	Area V4t
	FST	Area FST
	V3CD	Area V3CD
	LO3	Area Lateral Occipital 3
6 Early Somatosensory and Motor Cortex	4	Primary Motor Cortex
	3b	Primary Sensory Cortex
	1	Area 1
	2	Area 2
	3a	Area 3a
7 Sensori-motor associated paracentral lobular and mid cingulate cortex	5m	Area 5m
	5mv	Area 5m ventral
	23c	Area 23c
	5L	Area 5L

	24dd	Dorsal Area 24d
	24dv	Ventral Area 24d
	SCEF	Supplementary and Cingulate Eye Field
	6ma	Area 6m Anterior
	7Am	Medial Area 7A
8 Premotor Cortex	FEF	Frontal Eye Fields
	PEF	Premotor Eye Field
	55b	Area 55b
	6d	Dorsal Area 6
	6v	Ventral Area 6
	6r	Rostral Area 6
	6a	Area 6 Anterior
9 Posterior Opercular Cortex	43	Area 43
	OP4	Area OP4/PV
	OP1	Area OP1/SII
	OP2-3	Area OP2-3/VS
	FOP1	Frontal Opercular Area 1
10 Early Auditory Cortex	A1	Primary Auditory Cortex
	52	Area 52
	RI	RetroInsular Cortex
	PFcm	Area PFcm
	PBelt	ParaBelt Complex
	MBelt	Medial Belt Complex
	LBelt	Lateral Belt Complex
11 Association Auditory Cortex	TA2	Area TA2
	STGa	Area STGa
	A5	Auditory 5 Complex
	STSda	Area STSd Anterior
	STSdp	Area STSd Posterior
	STSvp	Area STSv Posterior
	A4	Auditory 4 Complex
	STSva	Area STSv Anterior
12 Insular and Frontal Opercular Cortex	PoI2	Posterior Insular Area 2
	FOP4	Frontal Opercular Area 4
	MI	Middle Insular Area
	Pir	Pirfom Cortex
	AVI	Anterior Ventral Insular Area
	AAIC	Anterior Agranular Insula Complex
	FOP3	Frontal Opercular Area 3
	FOP2	Frontal Opercular Area 2
	PoI1	Area Posterior Insular 1
	Ig	Insular Granular Complex
	FOPS	Area Frontal Opercular 5
	PI	Para-Insular Area

13 Medial Temporal Cortex	EC	Entorhinal Cortex
	PreS	PreSubiculum
	H	Hippocampus
	PeEc	Perirhinal Ectorhinal Cortex
	PHA1	ParaHippocampal Area 1
	PHA3	ParaHippocampal Area 3
	TF	Area TF
	PHA2	ParaHippocampal Area 2
14 Lateral Temporal Cortex	TGd	Area TG Dorsal
	TE1a	Area TE1 Anterior
	TE1p	Area TE1 Posterior
	TE2a	Area TE2 Anterior
	TE2p	Area TE2 Posterior
	PHT	Area PHT
	TGv	Area G Ventral
	TE1m	Area TE1 Middle
15 Sensory “bridge” regions of the temporal-parietal-occipital junction	PSL	PeriSylvian Language Area
	STV	Superior Temporal Visual Area
	TPOJ1	Area TemporoParietoOccipital Junction 1
	TPOJ2	Area TemporoParietoOccipital Junction 2
	TPOJ3	Area TemporoParietoOccipital Junction 2
16 Superior parietal and IPS cortex	7Pm	Medial Area 7P
	7AL	Lateral Area 7A
	7Am	Medial Area 7A
	7PI	Lateral Area 7P
	7PC	Area 7PC
	LIPv	Area Lateral IntraParietal Ventral
	VIP	Ventral IntraParietal Complex
	MIP	Medial IntraParietal Area
	LIPd	Area Lateral IntraParietal Dorsal
	AIP	Anterior IntraParietal Area
17 Inferior parietal cortex	PFt	Area PFt
	PGp	Area PGp
	IP2	Area IntraParietal 2
	IP1	Area IntraParietal 1
	IP0	Area IntraParietal 0
	PFop	Area PF Opercular
	PF	Area PF Complex
	PFm	Area PFm Complex
	PGi	Area PGi
	PGs	Area PGs
18	RSC	RetroSplenial Complex

Posterior cingulate cortex	POS2	Parieto-Occipital Sulcus Area 2
	PCV	PreCuneus Visual Area
	7m	Area 7m
	POS1	Parieto-Occipital Sulcus Area 1
	23d	Area 23d
	v23ab	Area Ventral 23 a+b
	d23ab	Area Dorsal 23 a+b
	31pv	Area 31p Ventral
	ProS	ProStriate Area
	DVT	Dorsal Transitional Visual Area
	31pd	Area 31pd
	31a	Area 31a
19 Anterior Cingulate and Medial Prefrontal Cortex	p24pr	Area Posterior 24 Prime
	33pr	Area 22 Prime
	A24pr	Area Posterior 24 Prime
	p32pr	Area p32 Prime
	a24	Area a24
	d32	Area Dorsal 32
	8BM	Area 8BM
	p32	Area p32
	10r	Area 10r
	9m	Area 9 Middle
	10v	Area 10v
	25	Area 25
	s32	Area s32
	pOFC	Posterior OFC Complex
	a32pr	Area Anterior 32 Prime
	p24	Area Posterior 24
20 Orbital and Polar frontal cortex	47m	Area 47m
	10d	Area 10d
	a10p	Area Anterior 10p
	10pp	Polar 10p
	11l	Area 11l
	13l	Area 13l
	OFC	Orbital Frontal Complex
	47s	Area 47s
	p10p	Area Posterior 10p
21 Inferior frontal cortex	44	Area 44
	45	Area 45
	47l	Area 47l (47 Lateral)
	a47r	Area Anterior 47r
	IFJa	Area IFJa
	IFJp	Area IFJp
	IFSp	Area IFSp
	IFSa	Area IFSa

	TGv	Area TG Ventral
22	SFL	Superior Frontal Language Area
Dorsolateral prefrontal cortex	8Av	Area 8Av
	8Ad	Area 8Ad
	8BL	Area 8B Lateral
	9p	Area 9 Posterior
	8C	Area 8C
	p9-46v	Area Posterior 9-46v
	46	Area 46
	a9-46v	Area Anterior 9-46v
	9-46d	Area 9-46d
	9a	Area 9 Anterior
	i6-8	Inferior 6-8 Transitional Area
	s6-8	Superior 6-8 Transitional Area

Appendix D: Results of Regional Distribution of Homotopic Coupling Abnormalities Analysis

Table A-2

Regional Effects of Group and Scan Type on Homotopic Coupling Activity

Section	Condition		Mean	SD	p-FDR
1 V1	Scan Type	Movie-driven	1.523	.430	.000
		Resting-state	1.940	.404	
	Group	PWE	1.720	.528	.898
		Controls	1.72	.397	
	Interaction				.369
2 Early Visual Cortex	Scan Type	Movie-driven	1.324	.335	.000
		Resting-state	1.773	.340	
	Group	PWE	1.593	.403	.409
		Controls	1.508	.390	
	Interaction				.187
3 Dorsal Stream	Scan Type	Movie-driven	.953	.206	.000
		Resting-state	1.208	.296	
	Group	PWE	1.135	.276	.171
		Controls	1.045	.281	
	Interaction				.659
4 Ventral Stream	Scan Type	Movie-driven	.798	.230	.000
		Resting-state	1.093	.279	
	Group	PWE	.930	.292	.843
		Controls	.918	.272	
	Interaction				.577
5 MT+ Complex	Scan Type	Movie-driven	.7875	.23760	.000
		Resting-state	.9879	.25697	
	Group	PWE	.900	.304	.275
		Controls	.848	.214	
	Interaction				.982
6 Early Somatosensory and Motor Cortex	Scan Type	Movie-driven	1.151	.300	.000
		Resting-state	1.439	.350	
	Group	PWE	1.371	.408	.184
		Controls	1.229	.278	
	Interaction				.843
7 Sensori-motor associated paracentral lobular and mid cingulate cortex	Scan Type	Movie-driven	.808	.221	.045
		Resting-state	.900	.202	
	Group	PWE	.908	.204	.142
		Controls	.811	.212	
	Interaction				.843

8 Premotor Cortex	Scan Type	Movie-driven	.715	.218	.322
		Resting-state	.784	.270	
	Group	PWE	.795	.280	.2687
		Controls	.720	.203	
	Interaction				.6613
9 Posterior Opercular Cortex	Scan Type	Movie-driven	.355	.272	.0903
		Resting-state	.472	.246	
	Group	PWE	.439	.257	.5769
		Controls	.416	.278	
	Interaction				.3538
10 Early Auditory Cortex	Scan Type	Movie-driven	.629	.218	.5044
		Resting-state	.674	.251	
	Group	PWE	.687	.263	.3451
		Controls	.630	.207	
	Interaction				.0377
11 Association Auditory Cortex	Scan Type	Movie-driven	.824	.234	.6417
		Resting-state	.859	.255	
	Group	PWE	.849	.249	.8976
		Controls	.840	.236	
	Interaction				.5311
12 Insular and Frontal Opercular Cortex	Scan Type	Movie-driven	.464	.206	.000
		Resting-state	.603	.217	
	Group	PWE	.553	.245	.6517
		Controls	.531	.201	
	Interaction				.324
13 Medial Temporal Cortex	Scan Type	Movie-driven	.642	.245	.0305
		Resting-state	.769	.178	
	Group	PWE	.672	.227	.324
		Controls	.763	.222	
	Interaction				.8976
14 Lateral Temporal Cortex	Scan Type	Movie-driven	.519	.251	.1509
		Resting-state	.609	.210	
	Group	PWE	.574	.242	.8427
		Controls	.565	.229	
	Interaction				.1904
15 Sensory “bridge” regions of the temporal-parietal-occipital junction	Scan Type	Movie-driven	.737	.214	.0132
		Resting-state	.875	.285	
	Group	PWE	.852	.305	.3215
		Controls	.780	.214	
	Interaction				.6626
16 Superior parietal and IPS cortex	Scan Type	Movie-driven	.748	.197	.000
		Resting-state	.888	.207	
	Group	PWE	.854	.244	.3451
		Controls	.786	.173	
	Interaction				.8427

17 Inferior parietal cortex	Scan Type	Movie-driven	.378	.261	.0396
		Resting-state	.500	.237	
	Group	PWE	.478	.264	.3639
		Controls	.406	.240	
	Interaction				.4926
18 Posterior cingulate cortex	Scan Type	Movie-driven	.919	.194	.000
		Resting-state	1.081	.178	
	Group	PWE	1.020	.222	.5385
		Controls	.998	.183	
	Interaction				.9819
19 Anterior Cingulate and Medial Prefrontal Cortex	Scan Type	Movie-driven	.655	.221	.2078
		Resting-state	.744	.264	
	Group	PWE	.704	.263	.9424
		Controls	.713	.231	
	Interaction				.9819
20 Orbital and Polar frontal cortex	Scan Type	Movie-driven	.500	.268	.1901
		Resting-state	.590	.224	
	Group	PWE	.544	.268	.991
		Controls	.545	.227	
	Interaction				.8976
Inferior frontal cortex	Scan Type	Movie-driven	.381	.262	.018
		Resting-state	.248	.181	
	Group	PWE	.263	.192	.0305
		Controls	.249	.180	
	Interaction				.0505
22 Dorsolateral prefrontal cortex	Scan Type	Movie-driven	.746	.216	.3689
		Resting-state	.791	.202	
	Group	PWE	.827	.225	.088
		Controls	.715	.175	
	Interaction				.9708

Note. Results of 22 2x2 mixed model ANOVAs exploring the effect of group and scan type on homotopic coupling.

Significant p-FDR values are indicated with *.

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Presentations: Chadwick, C., Yeung, J., O'Reilly, M., Ladowski, D., Khan, A., Burneo, J., Steven, D., & Johnsrude, I. *Homotopic Coupling in Persons with Epilepsy using Movie-Driven and Resting-State fMRI.* (Conference poster). Canadian League Against Epilepsy 2019 Scientific Meeting, Winnipeg, MB.