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Movie-driven fMRI Reveals Network Asynchrony and Connectivity Alterations in Temporal Lobe Epilepsy

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

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Abstract

Mesial temporal lobe epilepsy (TLE) is the most common form of focal epilepsy and is often resistant to medication. Recent studies have noted brain-wide disruptions to several neural networks in so-called “focal” epilepsy, notably TLE, leading to it being recognized as a network disease. We aimed to assess the integrity of functional networks while they were simultaneously activated in an ecologically valid manner, using an actively engaging, richly stimulating audio-visual film clip. This stimulus elicits widespread, dynamic patterns of time-locked brain activity, measurable using functional magnetic resonance imaging. Thirteen persons with drug-resistant TLE (persons with epilepsy; PWE) and 10 demographically matched controls were scanned while at rest and while watching a suspenseful movie clip in a 3T MRI system. We observed idiosyncratic activation in several functional networks among PWE during movie-viewing. Activation time courses among PWE synchronized poorly with the highly stereotyped movie-driven BOLD fluctuations exhibited by controls [i.e., high inter-subject correlation (ISC)]. We also examined coupling (functional connectivity) among 10 canonical functional networks during resting-state and movie-viewing conditions. Whereas functional networks in healthy viewers segregate to support movie processing, the auditory and dorsal attention networks among PWE do not segregate as efficiently. Furthermore, we observed a robust pattern of connectivity alterations in temporal and extratemporal regions during movie viewing in PWE compared to controls. Our findings supplement evidence derived from resting-state fMRI and provide novel insight into how the cognitively engaged brain is altered in TLE.

Keywords: Temporal lobe epilepsy, fMRI, naturalistic stimulation, resting-state networks, inter-subject correlation, functional connectivity

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List of Abbreviations

BOLD	Blood-oxygen-level dependent
DAN	Dorsal attention network
DMN	Default mode network
EEG	Electroencephalography
FC	Functional connectivity
FDR	False discovery rate
FP	Frontal pole
fMRI	Functional magnetic resonance imaging
HG	Heschl's gyrus
ICA	Independent components analysis
IED	Interictal epileptiform discharges
ISC	Inter-subject correlation
LG	Lingual gyrus
MRI	Magnetic resonance imaging
OFusG	Occipital fusiform gyrus
PT	Planum temporale
PWE	Persons with epilepsy
ROI	Region of interest
Rs-fMRI	Resting-state functional magnetic resonance imaging
sLOC	Superior lateral occipital cortex
STG	Superior temporal gyrus
TLE	Temporal lobe epilepsy
toMTG	Temporo-occipital middle temporal gyrus

Chapter 1

Introduction

1.1 Epilepsy

Epilepsy is one of the most prevalent neurological disorders, affecting 50 million people of all ages worldwide and accounting for 0.6% of the global burden of disease (WHO, 2017).

Epilepsy is characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition (Fisher et al., 2014). Epileptic seizures are transient events that occur due to abnormal, excessive, and hyper-synchronous discharges of neuronal activity in the brain (Bromfield et al., 2013).

Approximately one third of people with epilepsy (PWE) present with seizures that are resistant to medications, meaning they do not respond appropriately to two or more anti-epileptic drugs (Kwan et al., 2010). Those with drug-resistant epilepsy rely on resective surgery to achieve seizure control (NICE, 2012; Jobst and Cascino, 2015).

Assessing surgical candidacy involves a number of methods to localize the area of the brain from which seizures originate (the seizure focus) for excision. These include taking a

medical history, conducting neuropsychological tests, using video-electroencephalography (video-EEG) monitoring to observe seizure semiology alongside electrical activity recorded across the scalp, and using various neuroimaging techniques such as magnetic resonance imaging (MRI) to detect structural abnormalities, and positron emission tomography (PET) and Single Photon Emission Computerized Tomography (SPECT) to visualize alterations in cerebral metabolism (Duncan et al., 2016). Despite these efforts, PWE may also undergo invasive recording using implanted (epidural, subdural or intracerebral) electrodes when non-invasive methods are discordant. These invasive methods are time-consuming, expensive and carry risks (King et al., 1997; Vale et al., 2013).

1.2 Temporal lobe epilepsy (TLE)

Mesial temporal lobe epilepsy (TLE) is both the most common and the most drug-resistant form of focal epilepsy (Spencer, 2002). In TLE, focal seizures originate in mesial temporal lobe regions (including the hippocampus, amygdala, parahippocampal gyrus, and entorhinal cortex). The hippocampus is a particularly epileptogenic structure and hippocampal sclerosis (HS), a lesion defined by cell loss and gliosis, is the hallmark histopathology of TLE (Blümcke et al., 2013). Seizures that begin in the mesial temporal lobes have been described to propagate preferentially through the ipsilateral lateral temporal neocortex (especially the posterior lateral temporal cortex) and the ipsilateral mesial frontal lobes (especially the orbitofrontal cortex) (Yoo et al., 2014; Liet, Dasheiff and Engel, 1991), after which they may undergo secondary generalization by spreading to contralesional cortical regions. The excitotoxicity of recurrent focal seizures and their secondary spread is a likely pathogenic mechanism for structural damage (Bonilha et al., 2010). Demonstrating the progressive adverse effects of recurrent seizures, Van Dellen and colleagues (2009) found that networks in the

temporal neocortex in TLE become more pathological over time, assuming more random and thus less optimal configuration, which might reflect a higher vulnerability to seizures. Patients with TLE often have a history of early-life onset, including febrile seizures or febrile status epilepticus (Patterson and Braman, 2014), which may have progressive consequences on brain network development. Early onset of TLE has been shown to be associated with substantial bilateral white-matter volume loss in temporal and extratemporal regions (Hermann et al., 2002), and network disruptions have been observed in children with TLE (Mankinen et al., 2012).

In addition to persistent focal seizures, PWE commonly exhibit impaired memory function and may endure other cognitive and psychiatric symptoms that persist through the inter-ictal periods. Memory impairment is the major cognitive comorbidity of TLE, with approximately 80% of persons with refractory TLE exhibiting impaired memory (Helmstaedter, Reuber, & Elger, 2002; Schwarcz & Witter, 2002). However, comorbidities also include impairments in language function, executive dysfunction including problem-solving and attention difficulties, as well as increased rates of depression and psychosis (Bragatti et al., 2010; Austin and Caplan, 2007; Bell, Lin, Seidenberg and Hermann, 2011; Campo et al., 2013; Kanner, 2008). With an early age of onset, recurrent seizures during development are associated with progressive memory impairment and global cognitive decline (Hermann et al., 2002; Lespinet et al., 2002). PWE consistently rate these deficits as impairing their quality of life to a greater extent than do seizures themselves (Johnson et al., 2004), yet these impairments are often untreated.

1.3 Epilepsy as a Network Disease

With the advent of advanced neuroimaging techniques such as functional magnetic resonance imaging (fMRI), researchers set out to investigate how a disease with supposedly focal

pathology could engender diverse and persistent comorbid symptoms. A rapidly evolving body of literature has revealed widespread alterations in brain network architecture, leading epilepsy to be recently characterized as a network disease (Jin, Jeong and Chung, 2015).

Resting-state functional magnetic resonance imaging (rs-fMRI) captures brain dynamics while subjects are at rest in the scanner. One way to assess brain network function is to measure the functional coupling or connectivity (FC) between the nodes (key regions) of a network. Two regions are said to be functionally connected when their blood-oxygen-level dependent (BOLD) signal fluctuations, measurable using fMRI, are highly correlated. When the time courses from multiple cortical regions show a stable coordinated pattern of activation, these regions are said to comprise a network. Functionally linked resting-state networks largely reflect the underlying white matter structure (van den Heuvel et al., 2009), although functional connectivity can also be found among brain regions not directly connected by corticocortical fibers (Honey et al., 2009).

A number of resting-state networks posited to be involved in cognition, affective behaviour, and attention remain coherent in the absence of an explicit task and their activity can be captured during rs-fMRI. These include auditory, visual, sensorimotor, default-mode, salience, dorsal-attention, and executive networks (Figure 1-1; Damoiseaux et al., 2006; Seeley et al., 2007). These resting-state networks are named based on their similarity in spatial extent and connectivity structure with various functional networks observed in task-based studies. These studies involve people performing distinct tasks that attempt to probe and characterize specific cognitive functions.

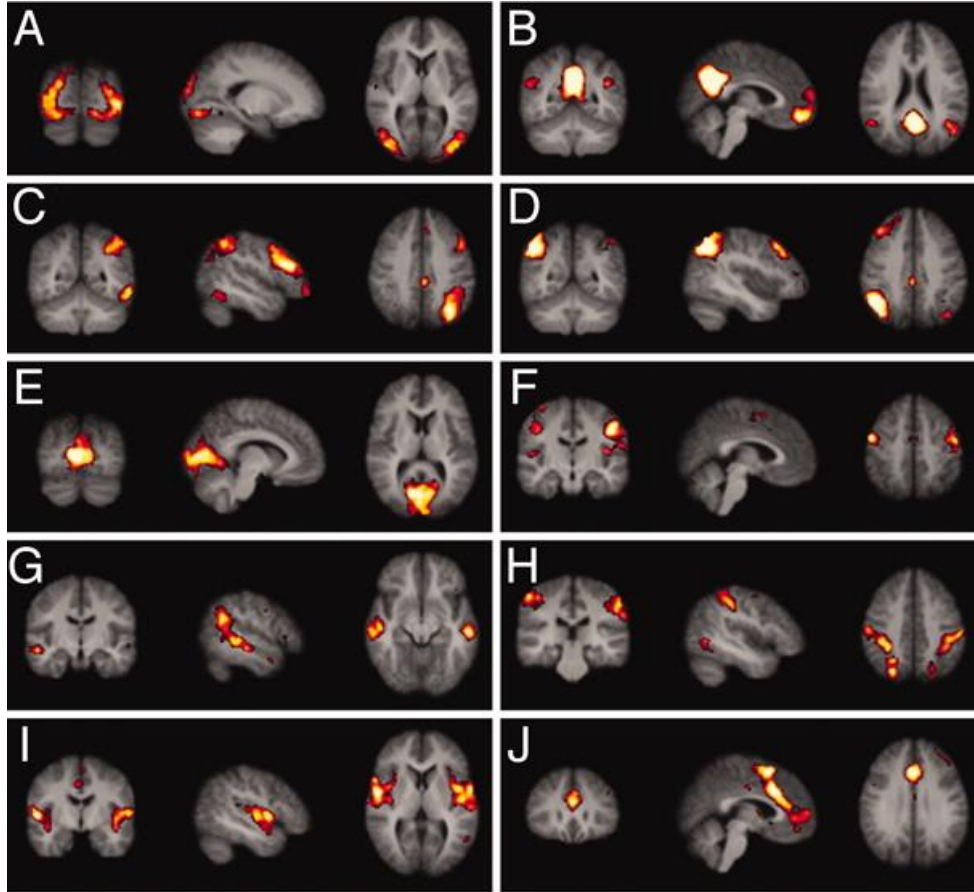


Figure 1-1. Canonical functional networks derived from rs-fMRI using independent components analysis (ICA). The networks depicted are (A) lateral visual, (B) default mode, (C) right frontoparietal, (D) left frontoparietal, (E) medial (primary) visual, (F) sensorimotor, (G) auditory, (H) dorsal attention, (I) salience, (J) central executive. Figure adapted from Damoiseaux et al. (2006).

Although not used clinically, rs-fMRI has been used extensively to examine the strength of functional relationships amongst brain areas in TLE. Early FC studies of TLE focused on identifying abnormalities within the epileptogenic network, comprising structures in the epileptic mesial temporal lobe (amygdala and hippocampus), adjacent cortices (entorhinal and lateral temporal cortex), and extratemporal structures including the thalamus and orbitofrontal cortex (Spencer, 2002). Consistent evidence of decreased resting-state FC in these regions emerged along with evidence of functional reorganization. For instance, Bettus et al. (2009) observed

decreased resting-state left hippocampal FC (anterior-posterior hippocampus coupling), and increased right hippocampal FC among persons with left TLE. The increased FC in the right hippocampus was positively correlated with performance on a standardized working memory battery among persons with left TLE, suggesting that this shift may reflect a compensatory mechanism.

Since the activity of a network is dependent on the functional interaction of its nodes, even focal disruption may cause dysfunction in global brain networks. In an effort to assess the extent of reorganization in TLE, recent work assessed connectivity beyond the mesial temporal lobes to examine widespread functional networks. Haneef et al. (2014) studied people with TLE and matched control participants and found that PWE exhibited increased connectivity relative to controls between the hippocampus and several areas of the limbic network (temporal lobe, insula, thalamus), frontal lobes, angular gyrus, basal ganglia, brainstem, and cerebellum; and reduced connectivity between the hippocampus and regions involved in perceptual networks (auditory, visual, sensorimotor) and with the precuneus, which is part of the default-mode network (DMN). Using independent components analysis (ICA), a data-driven separation technique that extracts spatially independent functional networks that are consistent across subjects, Zhang and colleagues found decreased FC in TLE within the auditory and sensorimotor perceptual networks and increased FC in the visual network (Zhang et al., 2009a), as well as decreased FC within higher-order dorsal attention, default-mode, and executive-control networks during rs-fMRI (Zhang et al., 2009b, 2010; see also Liao et al., 2010, 2011; Vlooswijk et al. 2011).

Relationships between networks also appear to be disrupted in epilepsy. The segregation and integration of distinct functional networks dynamically adapt to serve changing cognitive

demands (Cohen and D'Esposito, 2016). For instance, in the resting state, the DMN is activated and the dorsal attention network (DAN) is suppressed, while the opposite is true during cognitive engagement (Fox et al., 2005; Sridharan, Levitin and Menon, 2008). The salience network has been suggested to coordinate this reciprocal relationship (Sridharan, Levitin and Menon, 2008; Menon and Uddin, 2010). Abnormal interactions between these networks in the resting state were reported by de Campos and colleagues (2016) in persons with left and right TLE.

Additionally, Warren et al. (2006), using resting-state EEG-fMRI to assess network interactions in Lennox-Gastaut syndrome, a childhood-onset form of epilepsy associated with refractory seizures and cognitive impairment, observed reduced FC between the DAN and executive control network, both involved in the top-down control of attention, as well as increased FC between the DMN and DAN, which, as stated, are normally anti-correlated. These abnormal network interactions persisted through the interictal (between seizure) periods that were not marked by intermittent spike and wave activity, termed interictal epileptiform discharges (IEDs).

Su and colleagues (2015) examined connectivity within and between the nodes of several common perceptual and executive resting-state networks, among them, the default mode, executive control, frontoparietal, visual and sensorimotor networks (Figure 1-2) in persons with TLE. Consistent with the findings by Bettus et al. (2009), Su and colleagues found widespread weakened connectivity (shown in Figure 1, in blue) within the epileptogenic (right) hemisphere across a number of networks, and strengthened connections (orange) in the contralesional (left) hemisphere. This suggests that functional networks may reorganize to the healthy hemisphere to preserve global functioning. In summary, these studies provide evidence of diffuse connectivity changes in TLE extending beyond the mesial temporal lobes to include perceptual and executive-

control networks. These disruptions may help to explain the diverse cognitive and psychiatric comorbidities of epilepsy.

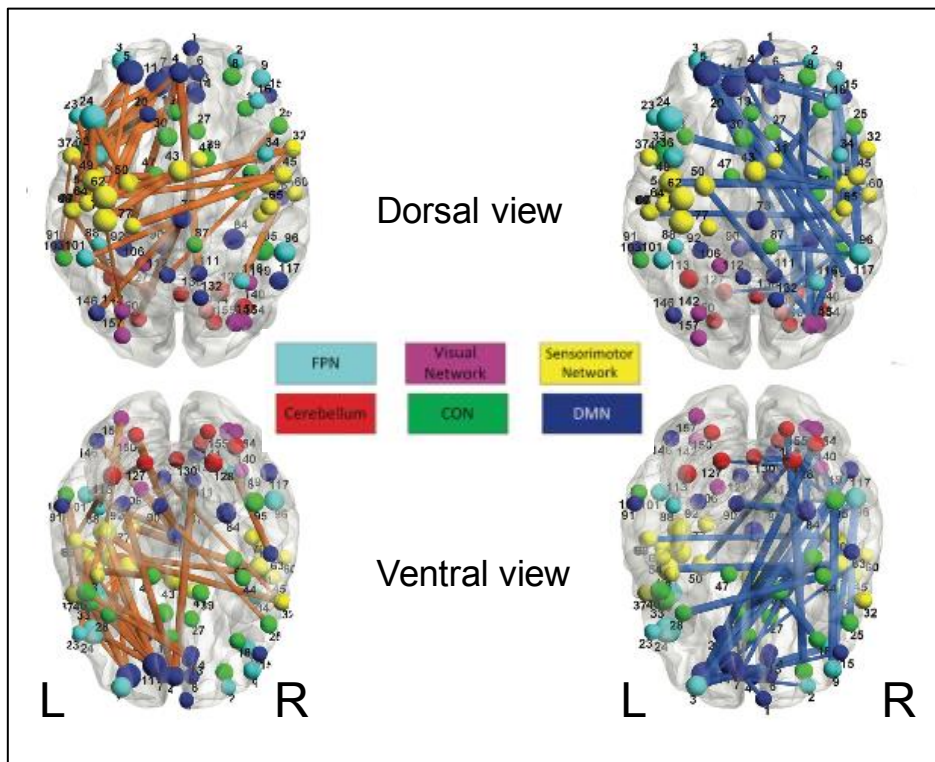


Figure 1-2. Widespread connectivity abnormalities in persons with right TLE compared to healthy controls. Network nodes are depicted in different colours. Strengthened connections in the contralesional left hemisphere are shown in orange and reduced connections in the epileptogenic hemisphere are shown in blue. Figure adapted from Su et al. (2015).

1.4 Task-Dependent Network Configuration

Given the body of literature describing network alterations in TLE during resting state activity, it is important to also assess these networks while they are actively engaged in naturalistic cognition. Limiting our investigation to the brain's spontaneous patterns of activity at rest may constrain our understanding of the complexities of important cognitive processes, such as language, attention and memory. That is, although functional networks remain coherent under task-free conditions, assessing these networks in the absence of an activating, driving stimulus limits our ability to meaningfully interpret the functional features of their activity.

Furthermore, the assumption that resting-state networks reflect cognitive network architecture has been challenged. Topological differences arise as neural networks flexibly adapt to support various cognitive states. Indeed, a number of studies have demonstrated dynamic network interactions that occur when healthy participants perform cognitive tasks relative to being at rest. For instance, Spadone and colleagues (2015) observed stronger connectivity between the visual network and DAN during a visuospatial attention task relative to rest. DeSalvo and colleagues (2014) on the other hand observed a diffuse pattern of weaker between-network connectivity during a decision-making task relative to rest. Cole and colleagues (2014), using a Human Connectome Project dataset of 115 subjects, compared the FC between 264 functional brain areas (from Power et al., 2011) during seven different cognitive task conditions (related to emotion, decision making, language, motor function, social cognition, working memory, and higher-order cognition) to that derived from resting state. On average, approximated 40% of connections were altered between rest and task conditions. Specifically, connections that were stronger during rest became weaker during task performance, and weaker resting-state connections were strengthened during task performance.

Incorporating many of the discrete cognitive abilities mentioned above, watching an engaging movie also demands dynamic reconfiguration of brain network connections (Bartels and Zeki, 2005; Betti et al., 2013; Emerson et al., 2015; Geerlig et al., 2015; Moussa et al., 2011). With these adaptations in mind, Davis and colleagues (2016) caution that the role of a region within a network cannot be inferred from its activity or connectivity pattern during rest, because its function varies depending on cognitive demands. These state-dependent network adaptations highlight the importance of studying neural networks not only during rest but across a range of mental states.

1.5 Naturalistic Stimulation

With the advent of functional neuroimaging, task-based paradigms were designed to test specific cognitive capacities, such as perception, attention, or memory. Particular cognitive constructs were assumed to exist modularly within the brain, facilitated by distinct regions. Relationships between task-activated regions were thus interpreted to be task-specific, rather than a manifestation of the intrinsic brain-wide networks that support the spectrum of human cognitive capacities (Power et al., 2011). Whereas traditional task-based fMRI paradigms target and provide insight into distinct constructs in isolation, natural cognition requires our simultaneous and interdependent recruitment of brain-wide networks to facilitate processing of competing cognitive demands.

An emerging technique that evokes and captures widespread cortical networks without making assumptions about their function is naturalistic stimulation. Naturalistic stimulation refers to complex dynamic stimuli, such as movies, video games, music or audio stories, that simulate real-life situations. Watching an engaging movie evokes reliable, time-locked, and functionally selective fluctuations in the BOLD signal throughout the brain, measurable using fMRI (Hasson et al., 2004; Bartels and Zeki, 2004; Hasson et al., 2010). Importantly, given the perceptual, attentional and executive demands of a highly engaging movie, such stimuli activate many functionally important networks at once, making movie-driven fMRI a highly efficient way to assess global functioning and network integrity in an ecologically valid manner.

Like rs-fMRI, naturalistic stimulation allows researchers to assess global network dynamics, but it also permits the measurement of stimulus-evoked responses afforded by task-based paradigms, as patterns of driven activation can be directly related to the perceptual and executive aspects of the movie stimulus. Unlike more reductionist, traditional cognitive tasks,

naturalistic stimulation does not require one to make assumptions about the elemental constructs of cognitive activity. Rather, it reveals patterns of functional activity that can be separated using data-driven methods, for instance, using ICA to extract distinct functional networks. ICA is well suited for exploring the neural dynamics of movie-driven fMRI as it is a non-parametric, multivariate, model-free technique that derives spatially distinct components of brain activity that are consistent across subjects (Calhoun et al., 2001; Ylipaavalniemi et al., 2009).

1.6 Inter-Subject Correlation (ISC)

Watching a highly engaging movie draws viewers into a shared experience. The guided cinematic experience is reflected in viewers' eye movements as they tend to track the same focal elements throughout a scene (Dorr et al., 2010, Hasson et al., 2008b). Moreover, engaging movies are also effective at driving shared neural response patterns across viewers. Indeed, brain regions spanning much of the cortical grey matter respond to an engaging movie in a highly similar fashion across viewers (Figure 1-3) (Hasson et al., 2010; Naci et al., 2014). That is, we observe synchronization of the distinct BOLD signal fluctuations from corresponding voxels across subjects under common naturalistic stimulation.

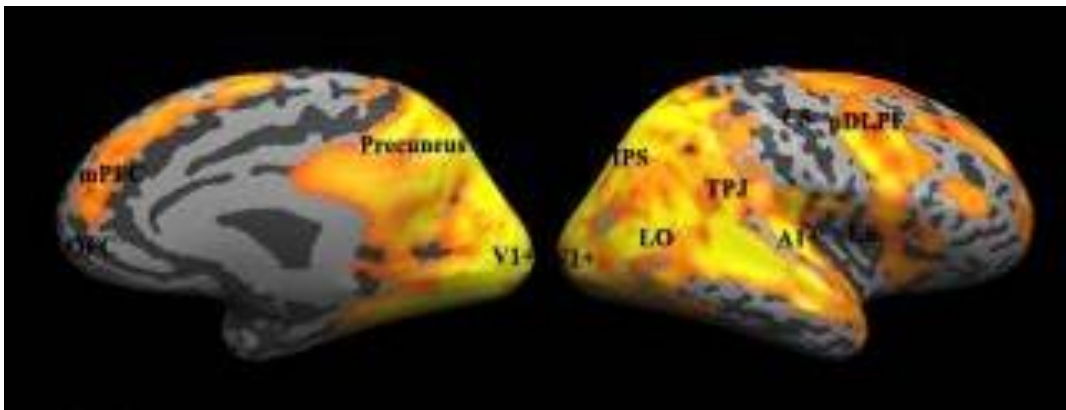


Figure 1-3. Voxels exhibiting significant inter-subject correlation (ISC) while subjects watched a clip from Alfred Hitchcock's suspenseful television episode "Bang! You're Dead". Figure adapted from Hasson et al. (2010).

This temporal synchronicity of neural activation across subjects under common naturalistic stimulation has been termed inter-subject correlation (ISC). ISC analysis (Hasson et al., 2004; Kauppi et al., 2010, 2014) is a model-free, data driven approach to detect the strength of voxel-wise correlations across subjects during free movie viewing. Unlike the heterogeneous BOLD signals captured across subjects during rs-fMRI, the inter-subject synchronization of brain activity during naturalistic stimulation delivers a reliable, neurotypical profile of stimulus-driven activation (Figure 1-4).

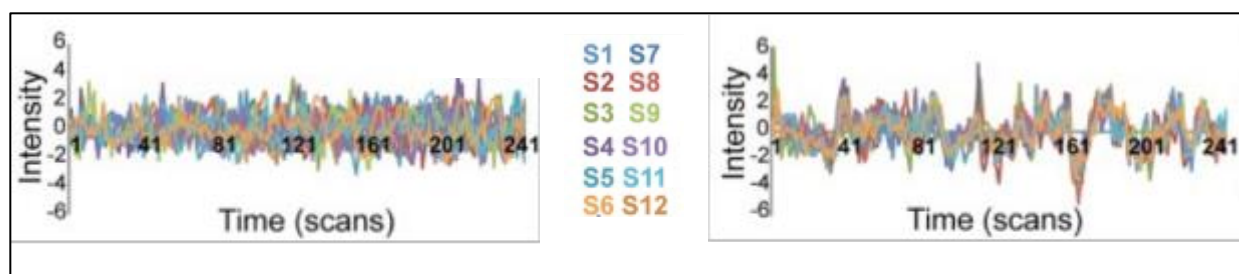


Figure 1-4. Cross-subject frontoparietal network time series are heterogeneous while at rest (left) and synchronized during movie viewing (right). Figure adapted from Naci et al. (2014).

Viewers share a similar response pattern not only in perceptual regions of auditory and visual cortex, but in higher-order brain regions responsible for processing the cognitive, emotional and attentional aspects of a highly engaging movie (Hasson et al., 2010; Naci et al., 2014). Importantly, the same neural networks commonly identified in the resting state can be extracted from movie-driven fMRI data using ICA. Naci and colleagues (2014) derived functional networks from healthy movie viewers using ICA and characterized the extent to which several neural networks were driven by the movie (Figure 1-5). They identified auditory (5-A), frontoparietal (5-B), visual (5-C), sensorimotor (5-D) and precuneus (5-E) networks that all exhibited significant ISC, demonstrating that an engaging movie is able to reliably drive both perceptual and high-order executive activity across viewers. The most engaging movie scenes tend to yield the highest degree of neural synchronization (Dmochowski et al., 2014), while disruptions to the story narrative tend to reduce how similarly viewers process its content

(Hasson et al., 2008b). Asynchronous responding tends to relate to poor comprehension (Hasson et al., 2009) and memory (Hasson et al., 2008a). The strength of ISC across networks is also functionally specific, such that a film's negative emotional valence is associated with increased ISC in emotion-processing areas (thalamus, ventral striatum, insula) and in the DMN, while scenes rated as highly arousing increase ISC in visual, somatosensory and dorsal attention networks (Nummenmaa et al., 2012).

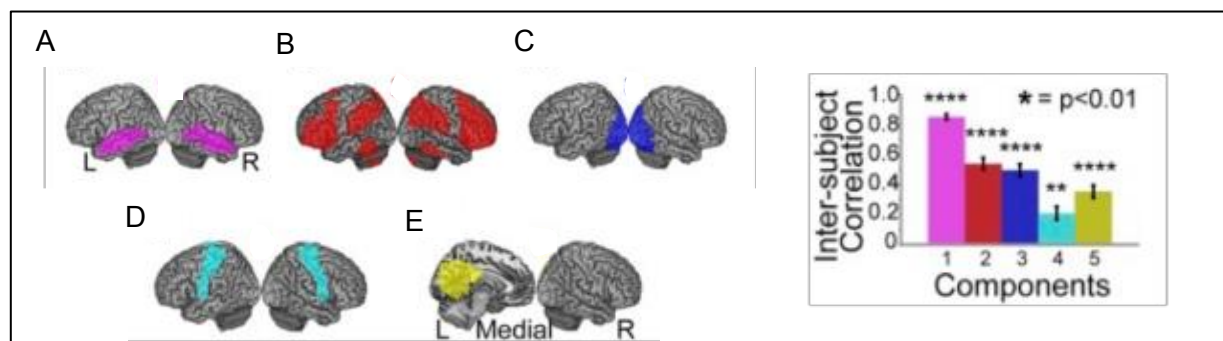


Figure 1-5. Functional networks exhibiting significant movie-driven ISC. A. auditory, B. frontoparietal, C. visual, D. sensorimotor, E. precuneus. Figure adapted from Naci et al., (2014).

Recent studies have used naturalistic stimulation to detect abnormal brain response patterns in several populations of interest. Adults with autism display neural activation characterized by idiosyncratic yet replicable responses compared to neurotypical controls (Hasson et al., 2009; Salmi et al., 2013). Older adults also display idiosyncratic response patterns posited to be related to attentional difficulties (Campbell et al., 2015). Hyett et al. (2015) observed that persons with melancholia exhibited weakened ISC in the right frontoparietal attention network while watching a negatively emotional film. Finally, Rikandi et al. (2017) found that abnormal precuneus activity during movie viewing classified persons with first-episode psychosis and was related to fantasy processing and severity of positive symptoms. These emerging clinical investigations highlight the potential for movie-driven fMRI to detect

global and network-specific abnormalities in clinical populations that can be related to behavioural and cognitive measures.

1.7 Benefits of Movie-Driven fMRI

A number of additional benefits afforded by naturalistic stimulation have been described in the literature. Firstly, head motion is a common fMRI artifact particularly relevant among children, older adults and clinical populations (Vanderwal et al., 2015; Huijbers et al., 2017). Head motion can introduce significant, systemic effects on intrinsic FC measures during rs-fMRI. Specifically, head motion has been found to decrease functional coupling across long-range connections, such as in the default mode and frontoparietal networks, while increasing local measures of functional coupling (Van Dijk et al., 2012; Power et al., 2012). In contrast to the low behavioural constraint of task-free resting state, watching a movie in the MRI scanner has been shown to decrease subject movement (Centeno et al., 2016; Huijbers et al., 2017; Vanderwal et al., 2015), likely owing to viewers' enhanced attentional engagement.

Secondly, the resting state has been found to be quite dynamic: during scanning, one's level of awareness varies over time between wakefulness and different sleep stages (Tagliazucchi and Laufs, 2014). These fluctuations affect FC strengths in several networks including regions involved in motor function, visual and auditory processing, executive function, and the default-mode network (Tagliazucchi and Laufs, 2014). Presenting a movie in the scanner has been shown to maintain wakefulness and attention in persons with epilepsy (Centeno et al., 2016). This may be particularly beneficial since IEDs, which in TLE are associated with transient deactivation in DMN regions (Gotman et al., 2005; Laufs et al., 2007; Shamshiri et al., 2017), are more frequent during sleep (Malow et al., 1998, *Epilepsia*).

Varying levels of wakefulness across subjects during resting-state imaging is undoubtedly one of the reasons why connectivity values derived from measurements during this unconstrained state vary substantially across people. But even while alert, different subjects may be in different cognitive states (i.e. engaging in different cognitive processes such as spontaneous thought, visual or auditory mental imagery, somatosensory awareness etc.), which have been shown to alter the connectivity patterns between functional networks (Doucet et al., 2012; Stoffers et al., 2015). In contrast, movie-driven fMRI results in individuals being alert throughout the duration of the movie, and results in their cognitive states varying synchronously as participants watch a movie under common stimulation.

Inter-subject variability in FC values has yet to be compared between rest and movie conditions, but naturalistic stimulation has been shown to improve intra-subject reliability relative to resting state. Wang et al. (2016) demonstrated that movie viewing improves test-retest reliability, increasing the stability of FC measures by approximately 50% when compared to conventional resting-state paradigms. Increased reliability during natural viewing was not only seen in perceptual networks, but in higher-order brain networks as well, including the DMN and DAN (Wang et al., 2016). The corollary of reduced variability is enhanced sensitivity to individual differences in FC patterns.

1.8 Research Question

The aim of this project is to demonstrate the value of a new, non-invasive imaging technique in which we use an actively engaging, richly stimulating audiovisual film clip to elicit widespread, dynamic patterns of brain activity in an ecologically valid manner. Our aim is to assess the activation and connectivity patterns of perceptual and executive networks as they process this multifaceted, naturalistic stimulus. We aim to examine individual functional

networks for asynchronous response patterns in persons with drug-resistant TLE relative to age-, sex- and education-matched neurologically normal controls. We hypothesize that the network timecourses of PWE will exhibit reduced synchronization (weaker inter-subject correlation) with those of controls. Next, we aim to investigate alterations in functional connectivity between these networks in PWE compared to controls. We anticipate that, among PWE, brain networks will exhibit a unique pattern of inter-connectivity during movie viewing compared to resting state. We additionally aim to evaluate whole-brain functional connectivity alterations in TLE during active engagement and resting state. We hypothesize that persons with TLE will exhibit disruptions in connectivity that will involve, but also extend beyond the epileptogenic temporal lobes. Finally, we aim to compare the degree of inter-subject variability in FC strengths between resting and movie conditions. We anticipate that, in addition to strong inter-subject correlation of voxel time courses, movie viewing will drive more similar patterns of connectivity between cortical regions. We hypothesize that we will observe reduced inter-subject variability of FC values in the movie condition relative to resting state for both PWE and controls, which may provide greater sensitivity to between-group differences.

We obtain fMRI data while PWE and demographically matched controls freely view a clip from Alfred Hitchcock's suspenseful television episode, "Bang! You're Dead," as used in previous studies (Hasson et al., 2010; Naci et al., 2014; Campbell et al., 2015), and while participants are at rest in the scanner. We derive the 10 canonical functional networks commonly described in the literature (Beckmann et al., 2005; Damoiseaux et al., 2006), namely, the auditory, medial and lateral visual, sensorimotor, default mode, dorsal attention, salience, left and right frontoparietal, and executive control networks using independent components analysis. For each participant, we evaluate each of the 10 network timecourses for their strength of ISC

with those timecourses in the remaining controls. Next, we compare the strength of coupling between the 10 networks (called inter-network connectivity) among PWE relative to controls in both movie and resting conditions. To gain a detailed picture of global connectivity abnormalities in TLE, we implement a whole-brain seed-to-seed functional connectivity analysis of the movie and resting state data, using 91 atlas-based seed regions from the Harvard-Oxford probabilistic atlas (<http://www.fmrib.ox.ac.uk/fsl/>; Desikan et al., 2006). Finally, we compare the inter-subject variability of FC values (between networks and between atlas-based seeds) derived from resting state and movie conditions in both PWE and controls.

Gaining a better understanding of the network abnormalities in TLE, and specifically, the patterns of alterations that arise in an actively engaged state, may help to explain patterns of cognitive impairment and psychiatric symptoms that impact the quality of life of PWE. We believe that movie-driven fMRI can provide novel insight into global network functioning in TLE that will complement the body of literature assessing networks in their resting state.

Chapter 2

Methods

2.1 Participants

Thirteen persons with TLE (5 female, mean age 37; Table 2-1) being evaluated for surgery and recruited from the Epilepsy Program at London Health Sciences Centre, participated in the study. We collected age of onset and medication record from each individuals' medical record. Clinical reports related to EEG recording, 1.5 Tesla MRI, PET, magnetic resonance spectroscopy (MRS), and histologic findings post anterior temporal lobectomy were also obtained, when available. These were used to determine the locus and pathological character of the epileptogenic lesion. We also recruited ten healthy volunteers approximately matched to the patients on sex, age, handedness and years of education (8 female, mean age 38; Table 2-2) from the London community. All participants provided informed consent. Ethical clearance was obtained from the Health Sciences Research Ethics Board of the University of Western Ontario.

PWE Clinical Variables

	Sex	Age	Handedness	Years of Education	Age of Onset	Epilepsy Duration	Pathology
1	M	48	R	18	45	3	Mild left hippocampal volume loss (MRI)
2	M	53	R	16	42	11	Left MTS and FCD (Histology)
3	F	26	L	14	2	24	Bilateral MTS (MRI)
4	M	21	R	12	19	2	MRI negative. Left hippocampal gliosis (Histology)
5	F	59	R	10	3	56	Left MTS and gliosis (Histology)
6	F	51	R	16	11	40	Right MTS (MRI)
7	M	52	R	10	4	48	Significant hypometabolism in the left TL (PET)
8	M	34	R	16	30	4	Cystic areas and volume loss in right hippocampus (MRI)
9	F	21	R	12	9	12	Subtle abnormality on right amygdala, suggestive of cortical dysplasia (MRI)
10	M	18	R	11	11	7	Extensive hypometabolism in left TL (PET) and potential left hippocampal volume loss posteriorly (MRI)
11	M	27	R	11	16	11	Subtle and minimal hyperintensity in bilateral mTL (FLAIR)
12	M	42	R	11	35	7	Left MTS. Mild cerebellar atrophy (MRI)
13	F	28	R	12	26	2	Equivocal right hippocampal changes

Table 2-1. Clinical variables for the 13 persons with temporal lobe epilepsy. (MTS: mesial temporal sclerosis. FCD: focal cortical dysplasia. FLAIR: Fluid attenuation inversion recovery. mTL: mesial temporal lobe.)

Control Variables				
	Sex	Age	Handedness	Years of Education
1	F	46	R	18
2	F	19	R	12
3	F	36	R	16
4	F	20	R	12
5	M	20	L	13
6	F	21	R	16
7	F	44	R	14
8	F	57	L	12
9	M	59	L	N/A
10	F	61	R	16

Table 2-2. Control demographic data.

2.2 Procedure

Participants completed measures of anxiety, depression, sleep quality and quality of life prior to entering the scanner. Volume acquisitions included: T1-weighted structural MRI, fluid attenuation inversion recovery (FLAIR) MRI, MRS, and diffusion tensor imaging (DTI), followed by fMRI (2 runs) in a 3 Tesla Siemens Prisma MR imaging system, according to the Eplink protocol (Ontario Brain Institute). Functional MRI data collection included 6 min 33 sec of resting-state imaging (with eyes closed), followed by 8 min during which participants watched an audiovisual film clip projected on a mirror box in the scanner. MR-compatible headphones (Sensimetrics, S14; www.sens.com) were used for sound delivery during the movie clip. The clip was the same edited version of a half-hour television episode (broadcast in 1961 entitled “Alfred Hitchcock Presents: Bang! You’re Dead,”) used in other studies (Hasson et al., 2008b; Naci et al., 2014; Taylor et al., 2015). Participants were instructed to watch the film carefully and follow the plot. Following the scan, participants completed a memory test for the content of the movie and a battery of standardized neuropsychological memory tests to complement other measures obtained during clinical testing. Post-scan testing took approximately 1 hour 20 min. Here, we

only report analyses of the two runs of functional imaging - resting-state and movie viewing - using the acquired T1-weighted structural MRI for image registration and localization.

2.3 Relevant Image Acquisition

An anatomical volume was obtained using a T1-weighted 3D rapid acquisition gradient echo (MPRAGE) sequence (32 channel coil, $1 \times 1 \times 1$ mm voxel size, 5 min 21 s acquisition time (TA), 900 ms inversion time (TI), 2.3 s repetition time (TR), 2.98 ms echo time (TE), $240 \times 256 \times 192$ matrix, 9 degrees flip angle (FA)). Functional images were acquired using gradient echo (GRE) echo planar imaging (EPI) (33 slices, $3 \times 3 \times 3$ mm voxel size, 25% interslice gap, 2,000 ms TR, 30 ms TE, 64×64 matrix and 75 degrees FA). The resting state run comprised 172 scans, and the movie run comprised 246 scans.

2.4 Imaging Preprocessing

Both movie and resting-state functional imaging data were preprocessed using Statistical Parametric Mapping 12 (SPM12; Wellcome Institute of Cognitive Neurology, www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the automatic analysis (“aa”) pipeline software (www.cusacklab.org). The processing steps we used included coregistration, image realignment, normalization to a template brain (MNI 152), spatial smoothing (10 mm FWHM Gaussian kernel) and application of a high-pass filter (1/128 Hz cutoff) to remove low-frequency noise. Before analyzing the movie and resting-state data, the first five dummy scans were discarded to ensure T1 equilibrium.

2.5 Independent Components Analysis

Spatial independent components analysis was performed using the Group ICA toolbox (GIFT v3.0a; <http://icatab.sourceforge.net/>). The results of an ICA depend on the number of components specified by the researcher to be separated by the algorithm, referred to as the dimensionality. The number of independent components to be extracted from the data was estimated using the minimum description length (MDL) criteria (Li, Adalı, & Calhoun, 2007). A mean estimate of 42 components (SD 12) was derived using all datasets. The mean estimates for patient was 44 (SD 12) and control 39 (SD 9). Forty components have been found to be most stable in studies using naturalistic stimulation (Pamilo et al., 2012; Lahnakoski et al., 2012), but Pamilo et al. (2012) also describe that the MDL estimate can overestimate the number of components due to smoothing in preprocessing and scanner noise. Overestimating the dimensionality can lead to component splitting, where a coherent network is split into subcomponents that correlate positively with each other (Backmann and Smith, 2004; Li, Adalı, & Calhoun, 2007). A lower 20-component dimensionality has been shown to generate well-matched functional networks between rest and task conditions (Smith et al., 2009), and has been used previously to derive coherent networks from movie-driven fMRI data (Naci et al., 2014). With these considerations in mind, we calculated 25 independent components, using the FastICA algorithm (Hyvärinen and Oja, 1997) in one group-level analysis on the movie-driven data that included all PWE and controls.

We then evaluated the reliability of the components using the ICASSO software (Himberg et al., 2003), a tool that is specialized for studying independent component estimates, implemented in GIFT. Solutions found with ICA algorithms tend to change slightly each time the analysis is run. This variability stems from the stochastic nature of the data and optimization

algorithm (Ylipaavalniemi, 2005). As such, ICA can produce different component estimates upon repeated runs. Running the FastICA algorithm several times allows for resampling of the data (through bootstrapping and randomizing initial conditions) on each run to allow the algorithm to converge on different decompositions. ICASSO was used to evaluate the reliability of these solutions across 10 ICA runs. It provided an R-Index (I_R) related to the similarity (absolute correlation) of the clusters across runs. A higher value of I_R (>0.8) indicates that the estimates were consistent, with a maximum value of 1 (Correa et al., 2007; Li, Adalı, & Calhoun, 2007).

There are three stages to Group ICA: group data reduction, ICA calculation, and back reconstruction. Initially, in GIFT, the image mean is removed from the data at each time point. Next, data reduction is performed using a two-stage Principal Components Analysis (PCA), first at the single-subject level and second at the group level on temporally concatenated data. Temporal concatenation allows for unique time courses for each subject but assumes common group spatial maps, whereas spatial concatenation allows for unique maps but assumes common time courses. The former has been found to be optimal for fMRI data because temporal variations in the BOLD signal are greater than spatial variations (Schmithorst and Holland, 2004). Reduced data then enter the forward estimation, which calculates spatially independent BOLD maps. Back reconstruction (using GICA3, as recommended by Erhardt and colleagues (2011)) provides estimates of the unique network spatial maps and time courses for each individual. The GICA3 method uses information retained from the PCA to derive the subject-specific component spatial maps and time courses. Finally, the voxel-wise time series within each participant's spatial map are converted to z-scores. The z-score reflects the degree to which

the time series of each voxel is associated with the mean time series of the specific spatial component within which it is located.

ICA analyses are effective for removing motion artifact because noise signals are split off into their own components (Kochiyama et al., 2005). Functional networks were identified through visual inspection of the spatial maps and time course power spectra (Kelly et al., 2010), removing components with non-neuronal spatial maps (outside the brain, skull or CSF) and with artefactual time course properties (high-frequency or saw-tooth pattern physiological noise). Networks with ICASSO stability values greater than 0.8 were selected for further analysis. We performed ten independent-samples t-tests in GIFT comparing the spatial maps of each network of interest between PWE and controls. To assess whether there were condition-dependent changes to the network spatial maps, we ran an additional ICA in GIFT including two sessions (movie and rest) and all participants (PWE and controls). We performed 10 paired t-tests on the unique spatial maps of the 10 networks of interest derived from movie and resting state.

2.6 Inter-Subject Correlation

To conduct the inter-subject correlation (ISC) analysis, each participant's z-transformed time course from each network of interest was extracted from the ICA and entered into a MATLAB matrix. For each network, we computed pair-wise correlations (Pearson's correlation coefficient, r) among controls to produce a distribution of ISC values representing the degree of network synchronization among healthy viewers. Next, each PWE's network time course was correlated with that of all controls and the mean of these correlations represented the degree to which a given PWE correlated with controls. Those PWE with mean ISC values two standard deviations below the mean among controls were identified as outliers, displaying asynchronous network activation.

2.7 Functional Connectivity

Functional connectivity analyses on both resting and movie data were conducted using the CONN toolbox for SPM (<http://www.nitrc.org/projects/conn>; Whitfield-Gabrieli and Nieto-Castanon, 2012). Preprocessing was the same for both data types (coregistration, motion correction, and normalization in “aa”). Individual realignment parameters from SPM and outliers defined by the Artifact Detection Tools (ART) toolbox (http://nitrc.org/projects/artifact_detect/) were entered as first-level covariates. Global grey matter, white matter and CSF masks were included as regressors to remove variance. The toolbox implemented the anatomical component-based noise correction (aCompCor), which, in contrast to global signal regression, allows for the interpretation of anticorrelations. We applied linear detrending, despiking, and band-pass filtering at 0.01 – 0.1 Hz (Gohel and Biswal, 2015) to reduce low-frequency drift and noise. To evaluate inter-network connectivity, the ICA spatial maps (mean, binarized z-maps, $|Z| > 1$ threshold) for the 10 networks of interest were entered as regions of interest (ROIs) in the CONN toolbox. In an additional exploratory analysis, we utilized the 91 cortical regions of the Harvard-Oxford probabilistic brain atlas (<http://www.fmrib.ox.ac.uk/fsl/>; Desikan et al., 2006) as seed regions and evaluated FC alterations amongst these regions in PWE relative to controls.

Average time series data from the spatial maps (one timeseries from each of the 10 networks) and atlas clusters (91 seed regions) were extracted from non-smoothed functional data separately for each participant. Connectivity (measured as bivariate correlation coefficients) was then assessed between networks, and between seed regions, to create two separate correlation matrices for each individual. With 10 networks, there are 45 unique correlation values in each individual’s inter-network correlation matrix, and with 91 seeds, there are 4095 unique correlation values in each individual’s seed-to-seed correlation matrix. Next, we performed

analyses at the group level, treating subjects as a random effect, in order to examine connectivity differences between conditions (movie and rest) and between groups. To account for multiple comparisons required due to multiple pairs of ROIs being tested in each analysis, a false discovery rate (FDR) correction at a threshold of $p < 0.05$ was applied to each analysis (Benjamini and Hochberg, 1995). This method implements an adaptive thresholding procedure that produces adjusted p-values. It begins by ranking all tests p-values in ascending order. The adjusted significance threshold for each test is equal to a given test's rank (i) divided by the total number of tests (N) and multiplied by the chosen significance threshold (α ; here, 0.05). Those tests whose p-values are less than or equal to this adjusted α -level are considered significant. This is equivalent to multiplying the ranked p-values by a factor of N/i , giving adjusted p-values, which are evaluated against the chosen α -level.

To evaluate whether inter-network coupling strengths change between movie viewing and rest conditions, we first ensured that we could identify the same networks in both movie and rest in the two groups. Then, to compare inter-network connectivity configurations between movie and rest, we conducted 45 paired t-tests, which compared, for each pair of networks, the connectivity values between movie viewing and rest across all subjects (within-subjects contrast; movie > rest). Next, to evaluate between-groups differences in inter-network connectivity, we conducted two separate between-subjects analyses (each comprising 45 independent samples t-tests; PWE > controls) on subjects' inter-network connectivity matrices, one contrast on the resting-state data and one contrast on the movie-driven data. Only one inter-network connectivity value was significantly different between groups, so we performed a follow-up 2x2 mixed analysis of variance (ANOVA) in SPSS to evaluate the changes in connectivity between these two networks with a between-groups factor (movie vs rest) and a within groups factor (PWE vs

controls). Finally, for the atlas-based analysis evaluating whole-brain functional connectivity differences between groups in each condition, we again conducted two separate between-subjects analyses (each comprising 4095 two-sided independent samples t-tests) on the connectivity coefficients for all pairs of the 91 cortical regions, one analysis on the resting-state data and one on the movie-driven data. Finally, we compared the proportion of functional connections exhibiting greater inter-subject variance (s^2) during resting state relative to movie viewing in both network- and atlas-based connectivity matrices.

Chapter 3

Results

3.1 Independent Components Analysis

Ten functional networks of interest, all with ICASSO I_R values greater than 0.8 indicating their stability, were extracted from the group ICA performed on movie-driven data: auditory, default mode, dorsal attention, medial visual, lateral visual, sensorimotor, salience, left frontoparietal, right frontoparietal, and central executive networks (Figure 3-1). The independent-samples t-test performed on each network's spatial map, comparing its spatial extent between groups, revealed no differences between PWE and healthy controls in any of the 10 network spatial maps (all p -FWE > 0.05 ; Height threshold $T = 6.31$, Extent threshold $k = 100$ voxels). Comparing the network spatial maps derived from movie and rest conditions across all subjects, the 10 paired t-tests revealed no differences in spatial extent between conditions (all p -FWE > 0.05 ; Height threshold $T = 6.31$, Extent threshold $k = 100$ voxels). There was significantly stronger auditory network activation during movie viewing compared to resting state in two regions: the right posterior superior temporal gyri (pSTG) (66 -18 2 mm; $T = 12.42$,

p-FWE = 0.000, K_E = 634 voxels) and the left pSTG (-60 -16 0 mm; $T = 11.53$, p-FWE = 0.000, K_E = 758 voxels); however, both regions fell within the spatial maps derived from movie and rest.

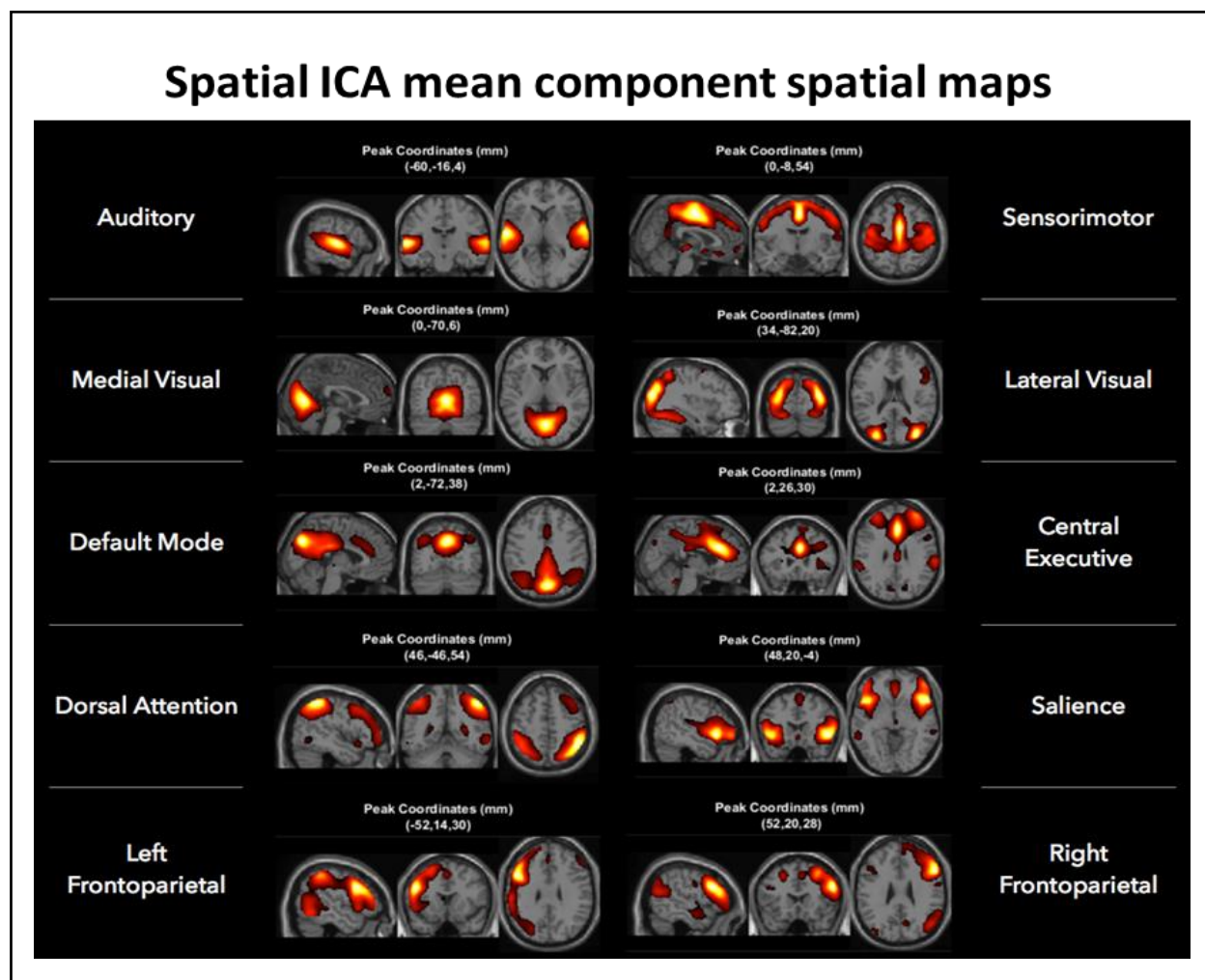


Figure 3-1. Group mean spatial maps for the 10 networks of interest derived from a 25-component group ICA ($n = 23$) on data acquired while participants watched an audiovisual film clip.

3.2 Inter-Subject Correlation

Inter-subject correlation analyses revealed asynchrony in a number of networks during movie viewing among PWE, including in the auditory (Figure 3-2), lateral visual, dorsal attention, and default mode networks (Table 3-1). The auditory network exhibited highly stereotyped activation among controls, having the strongest ISC (mean $r = 0.74$), and identified 7

of 13 PWE as outliers. The DMN, while having relatively low ISC among controls (mean $r = 0.26$), was the most sensitive network to abnormalities in PWE, identifying 9 of 13 as outliers, as well as one control. In order to examine whether differences in patients might be due to greater movement in this group, I took the absolute sum of the six motion parameters (x, y, z, pitch, roll, yaw) from the realignment stage of preprocessing and compared the mean and standard deviations between groups. Patients displayed less head motion during movie viewing (mean 185, SD 92) compared to controls (mean 203, SD 128).

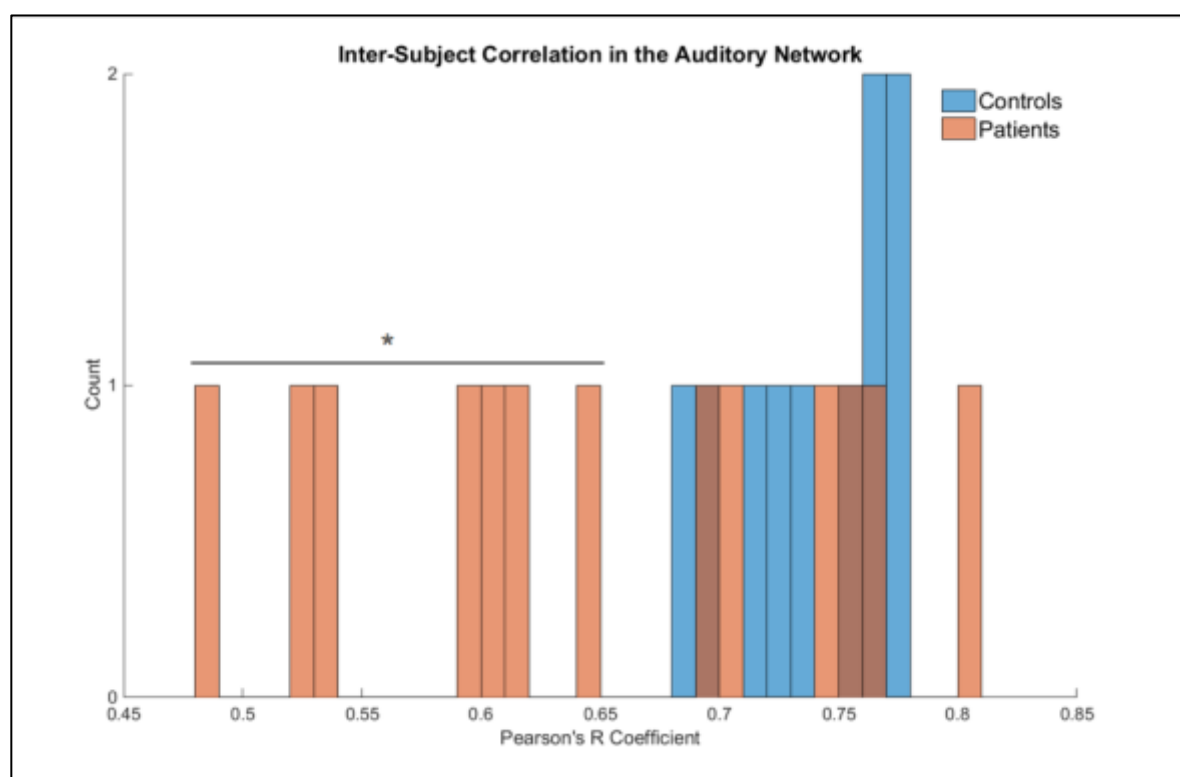


Figure 3-2. Inter-subject correlation in the auditory network. Seven patients were identified as outliers exhibiting weakened synchronization with healthy controls. Darker orange indicates a patient and control loading at the same correlation.

Inter-subject correlation in 10 networks of interest

Network	Mean ISC among Controls	Mean ISC among Patients	# of Patient Outliers	# of Control Outliers
Auditory	0.74	0.66	7	0
Lateral Visual	0.39	0.30	6	0
Dorsal Attention	0.29	0.20	5	1
Default Mode	0.26	0.18	9	1
Medial Visual	0.22	0.17	3	0
Central Executive	0.20	0.17	3	0
Left Frontoparietal	0.15	0.10	2	0
Saliency	0.12	0.10	0	0
Right Frontoparietal	0.11	0.10	2	0
Sensorimotor	0.05	0.03	0	0

Table 3-1. Mean inter-subject correlation values among controls and patients for each network of interest and the number of subjects identified as outliers from the control distribution. Mean ISC values are Pearson's r coefficients.

3.3 Inter-Network Connectivity

The results of our within-subjects contrast comparing inter-network connectivity between conditions across all subjects (PWE and controls) revealed a diffuse pattern of decreased connectivity between the 10 networks of interest during movie viewing compared to rest (Figure 3-3, Table 3-2). The auditory network exhibited decreased connectivity with all nine of the remaining networks during movie viewing compared to rest. The lateral visual network and DAN exhibited decreased connectivity with 6 remaining networks.

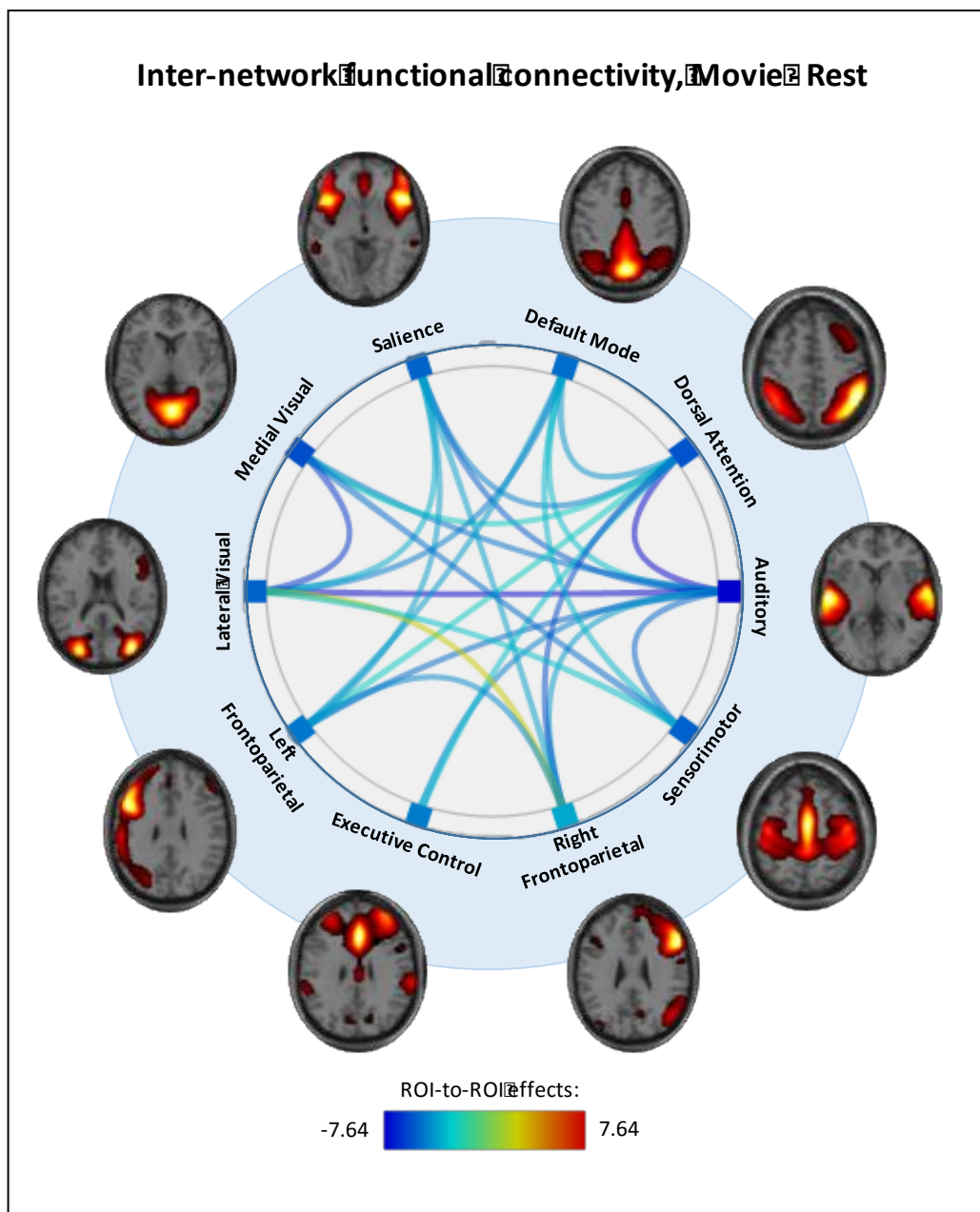


Figure 3-3. Decreased inter-network connectivity across all subjects during movie viewing compared to resting state. ROI-to-ROI effects are given as Fisher-transformed correlation coefficients (Z-values) representing effect sizes.

Inter-network connectivity analysis, connectivity differences across subjects during movie viewing relative to resting state (Movie – Rest)

Seed	ROI	T(21)	p-FDR
Auditory	Lateral Visual	-7.64	0.0000
	Dorsal Attention	-7.59	0.0000
	Saliency	-5.36	0.0001
	Sensorimotor	-5.22	0.0001
	Left Frontoparietal	-5.04	0.0001
	Medial Visual	-4.81	0.0001
	Central Executive	-4.49	0.0003
	Right Frontoparietal	-3.73	0.0014
	Default Mode	-2.92	0.0082
	Lateral Visual	Medial Visual	-6.32
Default Mode		-4.54	0.0005
Saliency		-3.27	0.0083
Sensorimotor		-2.83	0.0181
Right Frontoparietal		2.50	0.0313
Dorsal Attention	Right Frontoparietal	-5.74	0.0000
	Saliency	-4.51	0.0006
	Executive Control	-2.91	0.0151
	Left Frontoparietal	-2.28	0.0464
	Medial Visual	-2.24	0.0464
Right Frontoparietal	Left Frontoparietal	-4.18	0.0019
	Saliency	-3.60	0.0038
Left Frontoparietal	Default Mode	-3.72	0.0029
Medial Visual	Sensorimotor	-4.95	0.0003
Default Mode	Sensorimotor	-3.05	0.0137

Table 3-2. Weakened inter-network connectivity during movie viewing suggests greater network segregation to support processing of complex stimuli. p-FDR: the probability of making a Type 1 error (false positive) corrected for multiple comparisons (45 pair t-tests of network pairs) using the false discovery rate correction.

During resting state, we did not observe any significant differences in inter-network functional connectivity strength between groups ($p\text{-FDR} > 0.05$). During movie viewing, the between-groups contrast comparing the between-network coupling strengths of PWE relative to controls revealed strengthened connectivity between the auditory and dorsal attention networks among PWE, $T(21) = 3.80$, $p\text{-FDR} = 0.0073$. A 2x2 mixed ANOVA was conducted to evaluate the effect of condition (movie vs rest) and group (PWE vs controls) on the connectivity between the auditory and dorsal attention networks. A significant Condition X Group interaction [$F(1,21)$

= 5.619, MSE = 0.064, $p = 0.027$] (Figure 3-4) reflected the fact that between-network connectivity did not differ between PWE ($M = 0.214$, $SD = 0.341$) and controls ($M = 0.294$, $SD = 0.198$) in the resting state, whereas controls displayed stronger negative correlations ($M = -0.364$, $SD = 0.141$) in the movie condition than did PWE ($M = -0.089$, $SD = 0.192$), suggesting that the auditory and dorsal attention networks do not segregate to the same degree in PWE as in controls during movie viewing.

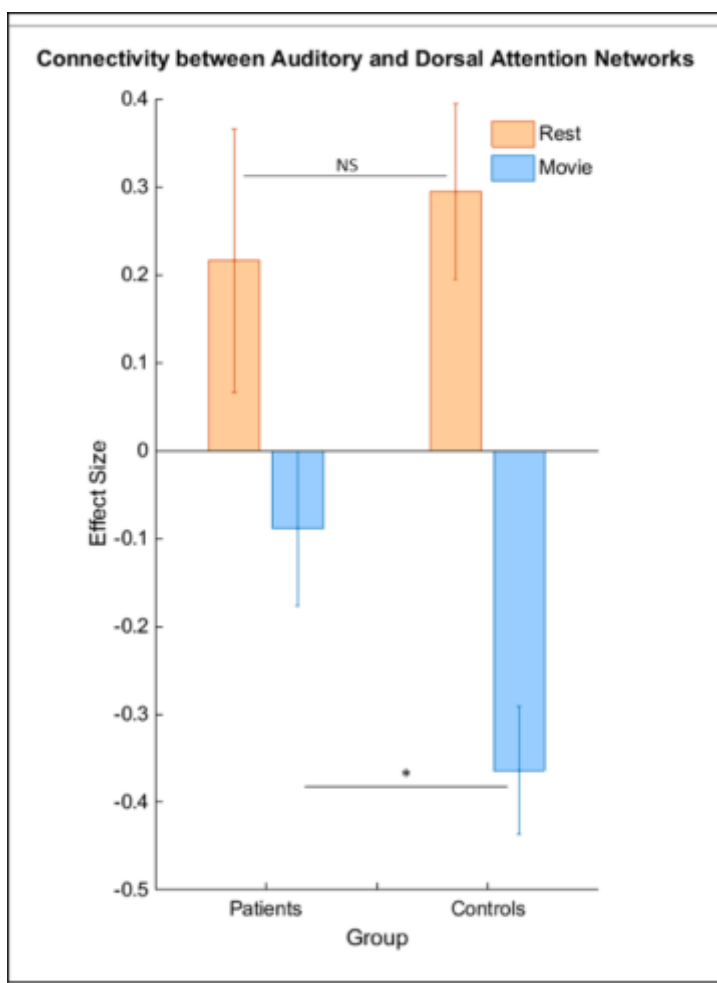


Figure 3-4. Connectivity between the auditory and dorsal attention networks. Results of a 2x2 mixed ANOVA reveal a significant Condition X Group interaction such that PWE did not differ from controls during resting state, while in the movie condition, PWE display weaker negative correlations between the auditory and dorsal attention networks than do controls. Effect size is measured as the mean Fisher Z-transformed correlation coefficient. Error bars indicate 90% confidence intervals. Variance was reduced within each group in the movie condition compared to resting state.

In comparing the degree of inter-subject variability in the FC values derived from the movie-driven data compared to the resting-state data, we found that the movie condition provided reduced inter-subject variance (s^2) in between-network and seed-to-seed correlation coefficients. Among controls, 3169 of the 4095 (77%) atlas-based seed-to-seed connections and 43 of the 45 (96%) inter-networks connections were more variable in resting state compared to the movie condition. Among patients, 3213 of the 4095 (78%) atlas-based connections and 42 of the 45 (93%) inter-network connections were more variable in rest. For instance, the inter-subject variance in the connectivity between the auditory and dorsal attention networks (Figure 3-4), was reduced in the movie condition for both groups compared to resting state (PWE $s^2_{rest} = 0.116$, $s^2_{movie} = 0.037$; Control $s^2_{rest} = 0.039$, $s^2_{movie} = 0.020$).

3.4 Global Functional Connectivity

Like the network-level analysis, the atlas-based analysis comparing the connectivity values across 91 cortical regions (defined by the Harvard-Oxford atlas) between PWE and controls (4095 independent samples t-tests), did not reveal any between-group functional connectivity differences during resting state (all $p\text{-FDR} > 0.05$). During movie viewing, however, PWE, relative to controls, exhibited weaker connectivity between the left posterior (temporo-occipital) middle temporal gyrus (toMTG) and bilateral temporal regions, and stronger connectivity between the left toMTG and occipital regions (occipital fusiform gyrus and lingual gyrus). PWE also exhibited stronger connectivity between the left superior lateral occipital cortex (sLOC) and left temporal regions, and between the right frontal pole (FP) and bilateral temporal regions relative to controls (Figure 3-5; Table 3-4).

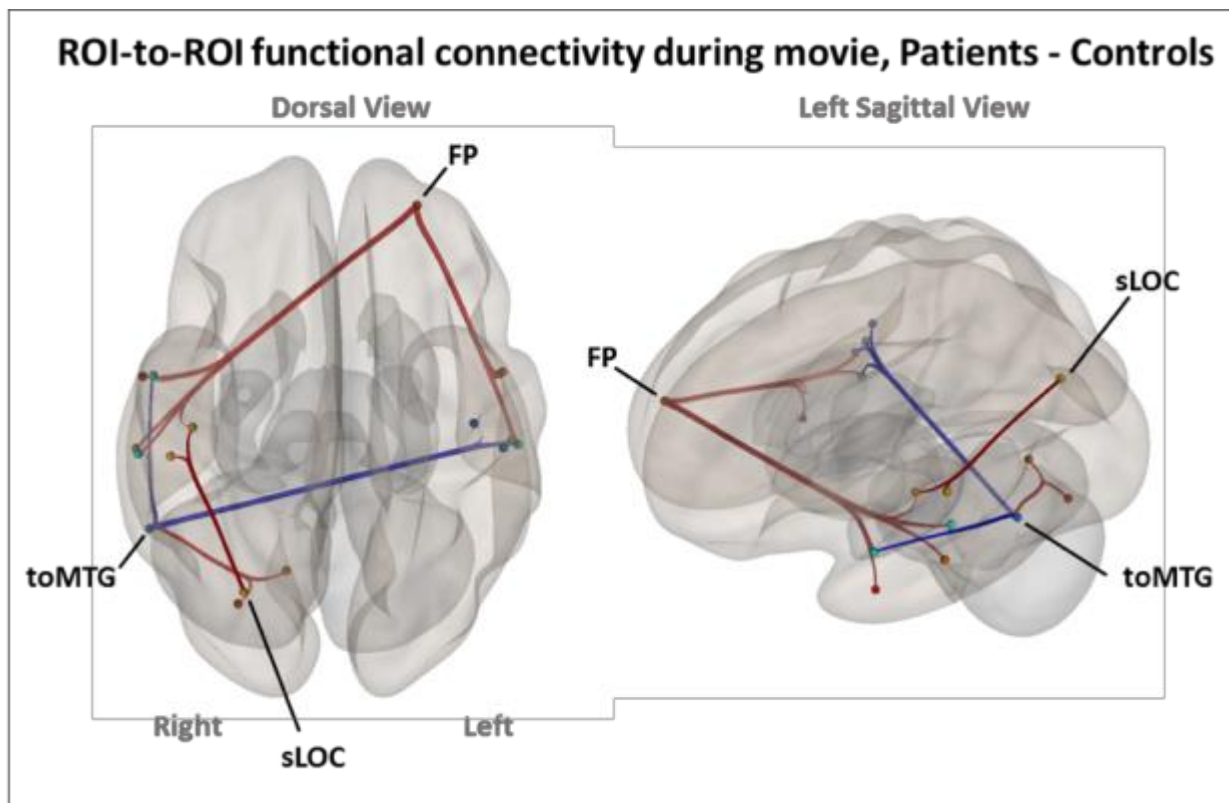


Figure 3-5. ROI-to-ROI analysis. Functional connectivity alterations in PWE relative to controls during movie viewing. Stronger connections (PWE > controls) are in red. Weaker connections (PWE < controls) are in blue.

ROI-to-ROI analysis, connectivity alterations in PWE relative to controls (PWE – Controls) during movie viewing

Seed	ROI	T(21)	p-FDR	
FP r	aMTG l	4.23	0.0215	
	pMTG r	4.07	0.0215	
	pSTG l	3.90	0.0215	
	pSTG r	3.84	0.0215	
	aSTG l	3.51	0.0376	
	aMTG r	3.34	0.0387	
	HG l	3.32	0.0387	
	aSTG r	3.27	0.0387	
	pMTG l	3.25	0.0387	
	toMTG l	pSTG r	-4.18	0.0379
		OFusG l	3.84	0.0391
		pMTG r	-3.53	0.0391
		pSTG l	-3.44	0.0391
		HG r	-3.36	0.0391
LG l		3.35	0.0391	
aSTG l		-3.35	0.0391	
PT l		-3.21	0.0478	
sLOC l	HG l	3.89	0.0384	
	PT l	3.89	0.0384	

Table 3-3. Cortical regions of the Harvard-Oxford atlas displaying altered connectivity among PWE relative to controls during movie viewing. FP: frontal pole, toMTG: temporo-occipital middle temporal gyrus, STG: superior temporal gyrus, HG: Heschl's gyrus, OFusG: occipital fusiform gyrus, LG: lingual gyrus, PT: planum temporale (Wernicke's area). p-FDR: the probability of making a Type 1 error (false positive) corrected for multiple comparisons using the false discovery rate correction.

Chapter 4

Discussion

4.1 Major Findings

Movie-driven fMRI is a rapidly administered, non-invasive tool for assessing functional networks in a naturalistic way. We demonstrate the utility of naturalistic stimulation to detect functional abnormalities in TLE in a data-driven and ecologically valid manner. We demonstrate that movie-driven fMRI reduces inter-subject variability of functional connectivity values relative to those derived across subjects during resting state, which likely provided strengthened sensitivity to group differences. The movie paradigm revealed asynchrony within and connectivity alterations among sensory and higher-order networks in PWE compared to matched neurologically typical individuals, whereas no group differences in connectivity were detected in the resting state condition.

4.2 Inter-Subject Correlation

We observed asynchrony in a number of functional networks during movie viewing among TLE patients, including in the auditory, lateral visual, dorsal attention, and default mode networks. Abnormalities in these networks have been reported in previous resting state and task-dependent fMRI studies (Haneef et al., 2014; Zhang et al., 2009a, 2009b, 2010, Liao et al., 2010). In light of the widespread alterations in functional connectivity described in the literature across a number of functional networks, it is perhaps unsurprising that we observe idiosyncratic response patterns in these networks. Indeed, previous work suggests that networks as a whole are more vulnerable in TLE. Wang et al. (2014) reported that the networks of patients with both right and left TLE were more vulnerable to targeted attacks and random failures in a robustness analysis relative to controls. Patients' networks suffered significant network breakdown across a wide range of removed nodes. Our results likewise suggest that a number of networks in TLE may be functionally disrupted. Disruptions to perceptual and higher-order networks may underlie the comorbid impairments in episodic memory, language function, and attention that frequently accompany TLE (Austin and Caplan, 2007; Campo et al., 2013).

Our sample of older healthy controls maintained the strongest ISC in the auditory network (mean $r = 0.74$), comparable to that found in younger adults by Naci et al. (2014) (mean $r = 0.8$) using the same ICA-derived approach. Our finding of slightly lower ISC values is likely due to our participants' age as healthy older adults display more variable responses to a driving stimulus, as described by Campbell et al. (2014). Nevertheless, our study revealed that the strength of ISC among healthy older adults was sufficiently sensitive to detect deviations from normality in our age-matched sample of TLE patients. Head motion is unlikely to have generated patients' low ISC with controls in the present study because our patient group displayed lower

motion parameters than did controls; however, head motion will be an important factor to consider in future studies.

The greatest number of patients in our study displayed asynchrony in the DMN. The functions of the DMN, while most commonly associated with self-referential thought (Davey, Pujol and Harrison, 2016), are only partly understood. It has been linked to autobiographical memory (Spreng, Mar and Kim, 2009), theory of mind (Buckner and Carroll, 2007), and tasks involving social content (Mars et al., 2012). Disruptions to this network are commonly reported in TLE. Liao et al. (2010) reported structural and functional abnormalities in the DMN in this population., finding that several DMN nodes showed a significant decrease in their number of connections to other regions. Recently, Robinson et al. (2017) assessed whole-brain resting-state dynamic functional connectivity in patients with TLE and healthy controls. They found that, whereas temporal stability characterized the healthy brain, patients with right and left TLE exhibited greater whole-brain instability, most consistently in the precuneus hub of the DMN, which may help to explain our findings of DMN idiosyncrasy.

DMN disruptions may have consequences on memory function. Assessing the DMN under naturalistic stimulation, Simony et al. (2016) examined the dynamic reconfiguration of the DMN during narrative comprehension. Using inter-subject functional correlation (ISFC), which measures the stimulus-dependent inter-regional correlations across subjects exposed to the same stimulus, they found that DMN coupling strength predicted viewers' memory for narrative segments. ISFC patterns in the DMN were locked to the temporal coherence of the narrative, with stronger correlations emerging during the intact narrative relative to a word scrambled version, highlighting the role of the DMN in information processing. Disrupted activation of the

DMN in TLE during naturalistic stimulation may lend insight into the memory impairments common among this population.

Our findings of widespread network asynchrony among persons with TLE may be due to the attentional difficulties often exhibited in this population (Fleck et al., 2002; Stella & Maciel, 2003). For instance, Zhang et al. (2009) showed that the functional connectivity of the dorsal attention network nodes during a top-down attention task is significantly lower in persons with TLE than in controls (see also Liao et al., 2010; Yang et al., 2010). Attentional difficulties may have contributed to our observed aberrant response patterns as suggested by Campbell and colleagues (2015), who found that older adults exhibited idiosyncratic response patterns during movie viewing, particularly in regions important for attentional control (i.e., superior frontal lobe and intraparietal sulcus) and language processing (i.e., bilateral middle temporal gyrus and left inferior frontal gyrus). PWE in our study may have been processing and interpreting the movie differently than controls, decreasing ISC across networks. Indeed, shared perspective taking has been demonstrated to increase ISC across viewers (Lahnakoski et al., 2014). Thus impaired attention may have led to a distributed pattern of abnormal activation.

4.3 Inter-Network Connectivity

In a group analysis including PWE and controls, we observed a distributed pattern of decreased inter-network connectivity during movie viewing compared to rest. The auditory, dorsal attention, and lateral visual networks exhibited the greatest proportion of weakened connections to other networks. These networks have been demonstrated to be strongly stimulus driven, displaying high ISC during movie-viewing (Naci et al., 2014). During external stimulation, networks may become more distinct or segregated in order to facilitate specialized information processing (i.e., process different aspects of the stimulus).

Our findings substantiate those found by Moussa et al. (2011), who observed a shift in the proportion of provincial hubs¹ and connector hubs² within the auditory network between multisensory stimulation (movie viewing) and resting states. The researchers found more connector hubs during resting state and more provincial hubs during movie viewing, demonstrating greater network segregation during active engagement. Geerligs et al. (2015) found similar decreases in connectivity within and between sensory networks during movie viewing compared to rest. Our findings of decreased inter-network connectivity across both perceptual and higher-order networks during active engagement compared to rest contribute to these observations and suggest that reorganization of network interactions supports real-world cognition.

We observed disrupted segregation of the auditory and dorsal attention networks among persons with TLE relative to controls during movie viewing. Using a similar ICA-driven approach, Jääskeläinen et al. (2008) demonstrated that the activation in the auditory network (comprising superior temporal regions including the superior and middle temporal gyri) during movie viewing correlated specifically with speech segments rather than music or natural non-speech sounds. The dorsal attention network is thought to mediate top-down attention, that is, subjects' voluntarily directed attention to a stimulus (Corbetta & Shulman, 2002). During movie viewing, the dorsal attention network has been implicated in spatial orientation (Nardo et al., 2016) and arousal (Nummenmaa et al., 2012). These networks are thus two strongly stimulus-driven networks engaged in processing specific aspects of the movie stimulus.

¹ Nodes that are well-connected within a module (here, within a network).

² Nodes making connections to other modules (here, to other networks).

Although we found that these two networks are positively correlated in both groups at rest, they become more strongly anti-correlated among controls during movie viewing. These networks are more weakly anti-correlated among PWE. We postulate that the networks of people with TLE either do not segregate as efficiently as do those of healthy controls during active engagement, or these networks maintain some degree of connectivity to compensate for within-network disruptions. Functional compensatory mechanisms in TLE are often proposed in the literature (Addis et al., 2007; Bettus et al., 2009; Maguire et al., 2001; Powell et al., 2007; Thivard et al., 2005; Zhang et al., 2010). Recent graph theoretical analyses in TLE have described a pattern of decreased global efficiency³ with increased local efficiency in functional (Wang et al., 2014) and structural (i.e., the underlying white matter tracts; Liu et al., 2014) connections. These observations indicate that TLE networks tend to be more regular and thus less optimal (Liu et al., 2014; Wang et al., 2014). Our findings may also demonstrate this sub-optimal regularity, whereby networks are unable to efficiently adapt to changing cognitive demands.

4.4 Global Functional Connectivity

Our findings contribute to the growing body of literature describing both temporal and extratemporal disruptions in TLE. We report patterns of (1) increased fronto-temporal connectivity, (2) decreased temporal connectivity, and (3) increased temporo-occipital connectivity during active engagement. We found abnormalities in functional connectivity that manifest as both increases and decreases in connectivity as well as unilateral and bilateral alterations. Although decreased connectivity and unilateral disruptions in TLE are often

³ The average inverse shortest path length in a network, suggested to be a measure of integration (Rubinov and Sporns, 2010).

described in the literature, our results are in line with a growing number of studies reporting increases in functional connectivity (McCormick et al., 2013; Voets et al., 2014; Bettus et al., 2010; Maccotta et al., 2013; Morgan et al., 2011; Liao et al., 2010) as well as bilateral alterations in ROI-to-ROI analyses (Wang et al., 2014; Bettus et al., 2009; Pereira et al., 2010; Campo et al., 2013).

4.4.1 Increased fronto-temporal FC

We observed strengthened coupling between right frontal cortex and bilateral temporal regions among PWE compared to controls during movie viewing. This finding complements the number of verbal and memory task-based studies that have observed abnormal frontal activation in TLE. During a verbal task, Maccotta et al. (2007) found that persons with left TLE disproportionately recruited right prefrontal cortex as compared with both controls and those with right TLE. Likewise, when performing a verbal episodic memory task, Dupont et al. (2000) observed increased frontal cortex activation in TLE compared to controls during the encoding phase. The authors suggest that the disruptions to the medial temporal memory system may have led patients to use a compensatory strategy, recruiting larger activation of the frontal cortex to support episodic memory. However, the PWE's performance was poor, suggesting that this reallocation was not efficient. This suggestion coincides with recent findings by Bigras et al. (2013) who found that lateralization of novel scene encoding to the right hemisphere in left TLE was associated with worse verbal memory performance.

Similar to the increased front-temporal pattern in TLE observed in our study, McCormick et al. (2014) observed a pattern of increased resting state connectivity between the prefrontal cortex and posterior regions of the DMN including bilateral inferior parietal lobule and bilateral temporoparietal junction among persons with TLE compared to controls. This strengthened

anterior-posterior pattern of connectivity was associated with worse verbal and visuospatial memory abilities among persons with left, and right, TLE respectively (McCormick et al., 2014). Considering these findings, we suggest that the abnormal pattern of coupling we observed may contribute to the language and memory deficits evident in PWE.

4.4.2 Decreased temporal FC

In PWE compared to controls, we observed weakened connectivity among temporal-lobe regions during movie viewing. The left MTG, which is implicated in language (Acheson and Hagoort 2013), semantic memory (Chao, Haxby and Martin, 1999), and multimodal sensory integration (Mesulam, 1998), displayed weakened coupling with primary auditory regions, including the superior temporal gyri (STG) and right Heschl's gyrus, as well as weakened coupling with language-related areas including the right MTG and left planum temporale (Wernicke's area). A number of studies have reported decreased FC between language related areas in TLE. Voets et al. (2009) observed reduced functional connectivity between bilateral middle temporal cortices; Xu et al. (2014) found reduced nodal efficiency (reduced intra-network connectivity) of the left STG and right MTG in TLE; and Pravatà et al. (2011) observed weakened functional connectivity within the language network, most notably in connections to the left posterior STG. Our findings identify the left MTG as an important node in TLE, here exhibiting weaker connections to other temporal regions involved in language and memory processing during active engagement.

4.4.3 Increased temporo-occipital FC

We found increased temporo-occipital connectivity during movie viewing in PWE compared to controls. There was increased coupling between the left MTG and primary visual

regions (left occipital fusiform gyrus and left lingual gyrus). There was also increased coupling between the left superior lateral occipital cortex, which plays a key role in object recognition (Grill-Spector, Kourtzi and Kanwisher, 2001), and the left planum temporale (Wernicke's area) and left Heschl's gyrus.

Lending insight into our observation of increased MTG connectivity with visual regions among PWE, previous studies have recognized the MTG as an important region in epilepsy for its connections to other networks. Wang et al. (2014) identified the MTG as a functional hub (i.e., a region exhibiting a high density of connections to other network regions) specific to persons with TLE relative to controls. Zhang et al. (2011), using graph-theory analysis, similarly reported stronger network involvement and centrality of the left MTG in idiopathic generalized epilepsy, with this region displaying greater connection and occupying a central location inter-connecting other regions. In addition, Liao et al (2010) found that the left MTG was more densely connected to other regions in persons with TLE compared to controls.

Previous studies have reported abnormal temporo-occipital connectivity in TLE during visual and verbal tasks. Assessing functional connectivity during a novel scene encoding task, Voets et al. (2009) observed a reverse pattern, reporting reduced temporo-occipital connectivity among persons with left TLE compared to controls. In line with these findings, Vannucci (2008) suggested that despite normal visual performance, persons with TLE may sub-optimally encode visual aspects of novel stimuli. Indeed, Yogarajah et al. (2008) found that persons with left TLE exhibited fewer connections between the parahippocampal gyrus and extrastriate occipital areas compared to persons with right TLE and controls. The authors note that animal models suggest that these connections aid in priming mesial temporal lobe structures to facilitate visual memory consolidation, and enhance the visual processing of emotionally significant stimuli. The notion

that visual memory encoding may be disrupted in TLE is behaviourally supported by recent findings that persons with TLE have difficulty recalling and reporting perceptual details when asked to describe the details of autobiographical memories or a perceptually rich film clip (St-Laurent et al., 2014; Lechowicz et al., 2016). Our findings of increased temporo-occipital FC among PWE may reflect a compensatory mechanism possibly employed during active engagement to facilitate cognitive processing and memory formation.

4.5. Comparison with Resting-State

Although we observed a distributed pattern of functional connectivity differences between groups during the movie condition, it is notable that no differences were detected during the resting state. This lack of sensitivity may be a consequence of insufficient resting state acquisition (6:33 min). Recent studies have found that the reproducibility and reliability of FC measures increase as a function of scan length, reaching a plateau after 13 min of rfMRI data (Birn et al. 2013; Gonzalez-Castillo et al. 2014). Conversely, in adults, analysis of incremental durations of resting state data ranging from 2 to 12 min reveal that functional connectivity estimates stabilize after approximately 5 to 6 min of data collection (Van Dijk et al., 2010). This acquisition time is thought to be adequate for detecting group-level differences (Laumann et al., 2015) despite individual-level analyses (distinguishing one individual from the group) benefiting from longer scanning to achieve sufficient sensitivity (Anderson et al., 2011; Hacker et al., 2013; Laumann et al., 2015; Pannunzi et al., 2017). Laumann and colleagues (2016) note that the connectivity structure of resting state fMRI remains nearly constant over minutes-long timescales. With this in mind, the absence of connectivity alterations in PWE during resting state in the present study may not be due to an insufficient acquisition period. Nevertheless, truncating our movie data to the equivalent scan time would test this speculation.

It is our view that the movie paradigm lends greater sensitivity to connectivity disruptions than that afforded by resting state, as seen in our small sample. Movies have been found to be more sensitive and specific to connectivity between anatomically connected regions than is resting-state imaging such that anatomically connected regions increased their correlations and regions not anatomically connected decreased their correlations during movie viewing compared to rest (Bartels and Zeki, 2005). Using a sliding-window correlation analysis, Elton and Gao (2015) observed task-related reductions in FC variability across time compared to resting state, most strongly for between-network interactions. Geerligs et al. (2015) proposed that constrained mental states may make it easier to detect differences between groups of participants. Indeed, Vanderwal et al. (2017) found that movies outperformed rest when employing an unsupervised test-retest matching algorithm to identify individual subjects from the group based on their FC patterns. Using 2s incremental increases in scan duration, the algorithm reached 100% accuracy using 4 min of movie-driven data, whereas the algorithm reached a ceiling accuracy of 90% using 5min 13s of resting-state data. The researchers suggest that using dynamic stimuli enhances the detection of individual differences in FC.

This research in line with our findings of greater inter-subject variability in FC values in the resting state relative to the movie condition for both PWE and controls. Of the 45 inter-network correlations, 42 and 43 were more variable among PWE and controls, respectively. Likewise, of the 4095 connectivity values in our atlas-based analysis, 3213 and 3169 were more variable among PWE and controls, respectively. Our results of reduced inter-subject variability not only in voxel-wise timecourses, as demonstrated by ISC, but in the connectivity between cortical regions, lend support to the idea that an engaging movie provides enhanced sensitivity to detect functional abnormalities particular to an individual or group.

4.6 Limitations

Our analyses were limited by our small sample size of 13 PWE and 10 controls. This may have limited our power to observe connectivity differences between groups during resting state. Our PWE group also had heterogeneous pathology, age of onset, and putative seizure laterality. Given the evidence for progressive structural and functional damage in TLE (as reviewed by Pitkanen and Sutula, 2002 and by Coan and Cendes, 2013), with a larger sample size we may have observed differences in connectivity between PWE with early relative to late onset, as found by Doucet et al. (2015). We may have also observed connectivity differences between PWE with left relative to right TLE, as demonstrated in the literature (Doucet et al., 2013; Pereira et al., 2013; Pail et al., 2010).

Interpretation of our ISC analysis is limited by the inter-dependence present between individuals' mean ISC values because each participant's timecourses are correlated with a largely overlapping group of control timecourses (Chen et al., 2016). This violates the independence assumption of parametric tests, making them unsuitable for group comparisons. Our classification of outliers as those patients with mean ISC values two standard deviations below the mean among controls might then be too liberal should our analysis underestimate the variability within the control distribution. Future studies would benefit from analyses employing bootstrapping or permutations testing to circumvent parametric assumptions.

4.7 Conclusion

We assessed the changes in networks activation patterns as well as functional connectivity both between networks and across whole-brain cortical regions among persons with drug-resistant TLE during natural viewing. Harnessing the inter-subject synchronization of

stimulus-evoked BOLD responses during natural viewing of an engaging movie, we observed asynchrony in a number of functional networks that distinguished individual PWE from the highly correlated signals among controls. We observed diffuse decreases in inter-network connectivity (i.e., increased network segregation) during movie viewing compared to rest across PWE and controls. However, we report impaired segregation between the auditory and dorsal attention networks among PWE compared to controls during movie viewing, in which these networks failed to segregate during active engagement to the extent that they do among controls. Our whole-brain FC analysis of the movie-driven data revealed patterns of temporal and extratemporal connectivity disruptions in PWE relative to controls among regions that have been implicated in verbal and visual processing as well as memory function.

Additionally, we report for the first time that movie-driven fMRI affords reductions in the inter-subject variability of FC strengths compared to those derived in the resting state. This observation suggests that movies may lend a more sensitive measure of group differences in FC due to the more reliable FC measures present across viewers. Indeed, no FC measures between our 10 networks of interest nor between the 91 atlas-based cortical regions were found to be significantly different between groups during the resting state, despite a robust pattern of alterations in TLE being revealed in our small sample during movie viewing.

To our knowledge, this is the first demonstration of the utility of movie-driven fMRI to investigate network integrity in epilepsy. This rapidly acquired, non-invasive method of functional neuroimaging affords the ease of acquiring global network dynamics offered by resting-state fMRI while providing reliable, stimulus-related cortical responses. Additionally, in contrast to traditional task-based fMRI paradigms, which rely on our conceptualization of distinct cognitive constructs, naturalistic stimulation enables the assumption-free assessment of

functional activation patterns. Given the perceptual, attentional and executive demands of the movie, we believe that movie-driven fMRI can provide novel insight into global functioning in TLE.

4.8 Future Directions

Activating neurocognitive networks simultaneously, movie-driven fMRI provides the opportunity to simultaneously assess language, attention, emotion processing, social cognition, among other cognitive capacities. Patterns of driven activation can be directly linked to aspects of the stimulus or subjects' performance on cognitive tasks related to the movie. Since natural viewing during movie-driven fMRI mimics naturalistic memory formation, we anticipate that this paradigm will be useful for studying the many facets of memory deficits that are prominent in this population. Importantly, this paradigm can be adapted for use with both adult and paediatric populations. Given the considerable functional reorganization evident in TLE, the movie paradigm may present a powerful clinical tool for elucidating the neural underpinnings of the diverse set of comorbid symptoms of epilepsy, as well as predicting cognitive outcomes following surgery.

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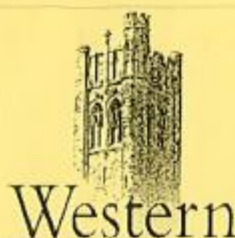
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Use of Human Subjects - Ethics Approval Notice

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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:

- changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
- all adverse and unexpected experiences or events that are both serious and unexpected;
- 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

Ethics Officer to Contact for Further Information

<input checked="" type="checkbox"/> Janice Sutherland (jsutherland@uwo.ca)	<input type="checkbox"/> Elizabeth Wambolt (ewambolt@uwo.ca)	<input type="checkbox"/> Grace Kelly (grace.kelly@uwo.ca)	<input type="checkbox"/> Denise Grafton (dgrafton@uwo.ca)
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This is an official document. Please retain the original in your files.

cc: ORE File
LHRI

Curriculum Vitae

Name: Alenka Bullen

Post-Secondary Education and Degrees:

The University of Western Ontario
London, ON, Canada
2015 – 2017
MSc Neuroscience

Queen’s University
Kingston, ON, Canada
2011 – 2015
BSc (Hons) Psychology

Honours and Awards:

Western Graduate Research Scholarship (WGRS)
The University of Western Ontario
2015 – 2017

Dean’s Honour List with Distinction
Queen’s University
2015

Dean’s Honour List
Queen’s University
2012 – 2014

Queen Elizabeth II Aiming for the Top Scholarship
Ontario Student Association
2011 – 2013

The John Stark Gilles Philosophy Book Prize
Queen’s University
2012

Scholarship for Leadership and Community Service
Municipal Retirees Organization
2012

Ottawa Ladies College Excellence Scholarship
Queen’s University
2011

Related Work: Graduate Teaching Assistant in Psychology
The University of Western Ontario
2015 – 2017

Writing Counsellor
Writing Support Centre, The University of Western Ontario
2015 – 2017

Research Assistant
Centre for Neuroscience Studies, Queen's University
2014 – 2015

Clinical Technician
Kingston Institute of Psychotherapy and Neurofeedback
2013 – 2015

Presentations:

Bullen, A., Naci, L., Khan, A., Johnsrude, I. (2016). *Using movie-driven fMRI to identify abnormal functional connectivity in intractable focal epilepsy.* (Conference poster). Canadian League Against Epilepsy 2016 Scientific Meeting, Quebec City, QC.

Bullen, A., Rob, M. & Levy, R. (2015). *Probing procedural strategy with a spatial working memory task: A potential marker of intact frontal function.* (Conference poster). 9th Annual Canadian Association for Neuroscience Meeting, Vancouver, BC.

Rob, M., Bullen, A. & Levy, R. (2015). *Differential effects of dopamine and selective dopamine agonists on spatial working memory, attention, learning and reaction time in healthy controls.* (Conference poster). 9th Annual Canadian Association for Neuroscience Meeting, Vancouver, BC.