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Inter-Subject Correlation Using Movie-Driven fMRI in Drug-Resistant Epilepsy

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Abstract

Treating drug-resistant epilepsy with surgery requires the localization of the epileptic focus. We explored the potential for movie-driven functional magnetic resonance imaging (fMRI) to act as a sensitive, non-invasive, and cost-effective tool to identify functionally disturbed networks. We assessed neural synchronization (inter-subject correlation; ISC) between presurgical epilepsy patients (n = 18) and healthy controls (n = 24) as they watched a suspenseful movie clip in the scanner. To optimize denoising, we compared ISC values with and without an automated Independent Components Analysis-based denoising step (ICA-AROMA). We found that denoising with ICA-AROMA elicited augmented correlation values, supporting its use for denoising naturalistic fMRI data. We identified abnormal overall ISC profiles in five of 18 patients and also observed region- and patient-specific ISC abnormalities. Naturalistic fMRI should be further explored for its utility as a sensitive and reliable complement to standard epilepsy surgical planning tools, potentially leading to improved treatment and outcomes.

Keywords

fMRI, inter-subject correlation, naturalistic stimulation, epilepsy

Summary for Lay Audience

Epilepsy is one of the most common chronic neurological disorders, affecting 1% of Canadians. Epilepsy is typically treated with medication, although nearly 1 in 3 people with epilepsy are resistant to medication. For these individuals, surgical intervention involving the removal of the parts of the brain thought to cause seizures may be a viable treatment option. Identifying the origins of epileptic activity is complicated by recent evidence that suggests seizures originate from within networks of interconnected brain regions, rather than from single discrete brain regions. It is possible that naturalistic functional magnetic resonance imaging (fMRI), which involves exposing subjects to complex audiovisual stimuli like movies while they undergo brain imaging, may be useful for identifying impaired networks in epilepsy. Research is needed to establish the clinical utility of naturalistic fMRI in presurgical evaluations of epilepsy.

In this investigation, we recruited 18 individuals with drug-resistant epilepsy being evaluated for possible surgery, and 24 healthy controls. Participants watched an 8-minute suspenseful movie clip while we recorded their brain activity with fMRI. To examine differences between patients and controls, we used a measure called inter-subject correlation (ISC), which provides a correlation value reflecting the extent of synchronization of neural activity at each brain region across people watching the same movie. By using this technique, we found abnormal overall ISC profiles in five out of 18 patients. Further, we identified regions that were particularly sensitive to abnormalities, and observed significant abnormalities in seven of 18 patients. We hoped that special software that accounts for head movements in the scanner would give us better results. We found that denoising with one such software known as ICA-AROMA resulted in larger correlation values, supporting its use with naturalistic fMRI data, particularly when the goal is to identify neural abnormalities in clinical samples. Overall, we anticipate that naturalistic fMRI paradigms will continue to be explored for their possible utility as sensitive and reliable complements to the surgical planning tools currently used in the presurgical evaluation of epilepsy, potentially leading to better treatment and improved outcomes.

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List of Commonly Used Abbreviations

ANOVA	Analysis of variance
AROMA	Automated removal of motion artefacts
BOLD	Blood-oxygen-level-dependent
CSF	cerebrospinal fluid
DTI	Diffusion tensor imaging
EEG	Electroencephalography
EZ	Epileptogenic zone
fMRI	Functional magnetic resonance imaging
FSIQ	Full-scale intelligence quotient
FWHM	Full width at half maximum
HC	Healthy control(s)
HCP	Human connectome project
ICA	Independent component analysis
ISC	Inter-subject correlation
LOO	Leave-one-out
mmp	Multi-modal parcellation
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
mTLE	Mesial temporal lobe epilepsy
MTS	Mesial temporal sclerosis
PET	Positron emission tomography
PWE	Person(s) with epilepsy
rs-fMRI	Resting-state functional magnetic resonance imaging
SPECT	Single photon emission computerized tomography
T	Tesla
TLE	Temporal lobe epilepsy
WM	White matter

Chapter 1

1 Introduction

For individuals with drug-resistant epilepsy, surgical resection of epileptogenic brain tissue may be a viable option for controlling seizures. Successful post-surgical outcomes rely upon the precise localization of the epileptic focus through rigorous multimodal evaluations. Recently epilepsy has been conceptualized as a 'network disorder'(Engel et al., 2013; Pittau & Vulliemoz, 2015; Richardson, 2012; Spencer, 2002). It is possible naturalistic functional magnetic resonance imaging (fMRI) paradigms, involving complex audiovisual stimuli like movies, may be useful complements to standard surgical planning tools for improving the identification of functionally disturbed networks in epilepsy. To establish the clinical utility of movie-driven fMRI, research is needed to evaluate such paradigms in conjunction with commonly used strategies for removing motion-induced signal variation from fMRI data (aka denoising). The optimization of the preprocessing of naturalistic fMRI is necessary to be able to make sensitive inferences about individual subjects. Here, I investigate the effects of an automated Independent Components Analysis-based denoising strategy (ICA-AROMA; Pruim et al., 2015b) on the temporal characteristics of movie-driven fMRI data derived in a clinical sample of people with epilepsy.

1.1 Epilepsy

Epilepsy is one of the most common chronic neurological disorders, affecting 1% of individuals in Canada (Téllez-Zenteno et al., 2004). Epilepsy exists when the brain demonstrates an enduring and pathological predisposition to generate seizures (Fisher et al., 2014). Epileptic seizures are transient occurrences resulting from an abnormal, excessive, and hypersynchronous discharge of neurons within the brain (Fisher et al., 2005). The brain regions involved in the generation and spread of epileptic activity make up the epileptogenic network. Epilepsy syndromes have traditionally been categorized as focal, with seizure generation and propagation circumscribed to one or a few localized foci within one cerebral hemisphere; or generalized, involving bilateral hemispheres and disrupting larger networks of brain activity (Fisher et al., 2017). Individual differences in the zone of epileptic origin and in patterns of abnormal neural

discharge throughout the cortex relate to differences in the cognitive and behavioural manifestations (semiology) of seizures.

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy diagnosed in humans, involving epileptic activity originating within the temporal lobe (Téllez-Zenteno & Hernández-Ronquillo, 2012). Mesial temporal lobe epilepsy (mTLE) accounts for the majority of cases of TLE and is characterized by epileptic activity that originates from a hippocampal or parahippocampal focus and is often associated with sclerosis of the hippocampus observable with magnetic resonance imaging (MRI; Babb et al., 1984; Engel et al., 1975). In individuals with mesial temporal sclerosis (MTS), seizures typically onset in childhood (Engel, 1996) and may result from the prolonged injurious effect of febrile seizures on the hippocampus (Lewis et al., 2002).

Epilepsy is primarily treated pharmacologically. For the majority of persons with epilepsy (PWE), medication offers effective seizure management. Nonetheless, seizures in 30-40% of adult PWE (and as many as 89% of individuals with MTS) are not well controlled with medication (Annegers et al., 1979; Cockerell et al., 1995; Del Felice et al., 2010; Kwan et al., 2010; Kwan & Brodie, 2000; Sander, 1993; Semah et al., 1998). Clinically, drug-resistant epilepsy can only be determined once a PWE has tried and tolerated at least two different kinds of medication but has not achieved seizure freedom (Kwan et al., 2010; Kwan & Brodie, 2000).

By and large, the chronic and often unrelenting course of epilepsy is associated with broad neurobiological, cognitive, psychological, and social consequences (World Health Organization, 2019). For individuals with drug resistant epilepsy, the surgical resection of brain tissue comprising the epileptogenic zone (EZ) may be a viable option for controlling seizures (Miller & Hakimian, 2013; Ramey et al., 2013; Thadani et al., 1995). Focal, compared to generalized, epilepsies are more commonly drug-resistant but are, fortunately, often amenable to surgical intervention (Kwan & Brodie, 2000; Mattson et al., 1996; Téllez-Zenteno et al., 2005).

1.2 Epilepsy as a Network Disorder

An emerging perspective in neuroscience is the idea that cognition arises from the joint function of distributed brain areas operating as large-scale 'networks'. The ability to precisely map functional networks with electrophysiology and neuroimaging during task-evoked settings and at rest has greatly advanced in recent years (Bandettini, 2012; Braga & Buckner, 2017; Friston, 2009; Gordon et al., 2017; Laumann et al., 2015; Power et al., 2011; Yeo et al., 2011). A number of functional networks have been identified thus far in healthy individuals, which support diverse functions from motor processing to top-down attentional control (Corbetta & Shulman, 2002; Dosenbach et al., 2007; Raichle et al., 2001). Network approaches have been eagerly adopted to evaluate functional neural reorganization in clinical samples (i.e., Baldassarre et al., 2016; Bassett & Bullmore, 2009; Gratton et al., 2012; Menon, 2011; Sheffield & Barch, 2016; Stam, 2014), like PWE (i.e., Gleichgerrcht et al., 2015; Gotman, 2008; Pittau & Vulliemoz, 2015).

The source of seizure generation in focal epilepsy is usually ascribed to a single pathological region (the 'seizure focus' or the EZ). However, an expanding body of evidence supports the perspective that 'focal' seizures may actually arise due to dysfunction within an 'epileptic network', comprising a broad set of functionally and anatomically connected cortical and subcortical brain regions (Engel et al., 2013; Pittau & Vulliemoz, 2015; Richardson, 2012; Spencer, 2002). Within a network framework, the conception of an EZ becomes broader, such that the removal of a hyperexcitable region can alter seizure generation and propagation within the entire affected network. Whole brain network (connectome) analyses using quantitative frameworks, like graph theory, have suggested surgically targeting cortical regions which link multiple brain systems and play a large role in overall network function ('hubs'; Power et al., 2013) might provide the greatest potential for reducing epileptogenic activity within an epileptic network (Engel et al., 2013; Goodfellow et al., 2016; He et al., 2017; Liao et al., 2016; Neal et al., 2020). Damage to, or resection of, hub regions may also result in more extensive neuropsychological deficits than might be expected from less well-connected regions (Warren et al., 2014). Without targeting hub regions within the epileptic network, the effective control of seizures with surgery is unlikely (De Tisi et al., 2011).

Evidence from observations of clinical seizure presentation, post-surgical outcome, histology, neuroimaging and electrophysiology supports the concept that epileptic seizures chronically alter brain activity within a network of regions not limited to the EZ, extending into widespread ipsilateral and contralateral structures (Gross, 2011; Kramer & Cash, 2012; Lemieux et al., 2011). Advances in neuroimaging and electrophysiology have been essential to examinations of epilepsy on a network level. Structural and functional neuroimaging studies support a network framework of focal epilepsy, confirming that epileptic activity cannot always be attributed to a single structure (Bartolomei et al., 2001; Bourien et al., 2004, 2005). In particular, structural neuroimaging studies in TLE have consistently shown extensive bilateral gray matter atrophy and white matter abnormalities in areas outside of the EZ, including the thalamus, cerebellum, cingulate gyrus, limbic structures (amygdala, fornix, entorhinal cortex), and parietal, frontal, and occipital lobes (i.e., Arfanakis et al., 2002; Concha et al., 2005; Focke et al., 2008; Govindan et al., 2008; Gross, 2011; Gross et al., 2006; Moran et al., 2001; Riederer et al., 2008; Spencer, 2002; Thivard et al., 2005, 2006; Yu et al., 2006). Investigations with single photon emission computerized tomography (SPECT) and positron emission tomography (PET) have revealed metabolic abnormalities in the temporal poles but also in the frontal lobes in people with TLE (Dupont et al., 2002; Semah et al., 1995). Resting-state fMRI (rs-fMRI) investigations in unilateral mTLE have revealed functional connectivity abnormalities within and between hippocampi (Bettus et al., 2009; Pereira et al., 2010; Pittau et al., 2012), as well as within several extra-temporal functional networks, including default-mode (Frings et al., 2009; Laufs et al., 2007; Liao et al., 2010; Zhang et al., 2010), attentional (Zhang et al., 2009a), perceptual (Zhang et al., 2009b), and language (Waites et al., 2006) networks. All such studies support the conceptualization of epilepsy as a network disorder, necessitating that we establish and advance network-oriented tools for the assessment and treatment of drug-resistant focal epilepsy

1.3 Presurgical Assessment in Epilepsy

The eligibility and success of surgical treatment for drug-resistant epilepsy depends on the accurate localization of the EZ and the careful mapping of eloquent cortex, thought to be responsible for functions like sensation, movement, language, and memory. Surgeons aim to

resect the minimum cortical area necessary to eliminate seizures, while preserving normal brain function to the highest degree. The extent of overlap between epileptogenic tissue and eloquent cortex must be determined to weigh the benefits of seizure reduction against the potential costs of neurocognitive post-surgical morbidity (Rosenow & Lüders, 2001).

Presurgical assessment in epilepsy relies upon extensive evaluations, consisting of comprehensive reviews of general and neurological medical history and video monitoring with whole-brain electroencephalography (EEG) to reveal information about semiology and location of seizure onset (Datta & Loddenkemper, 2011; Vakharia et al., 2018). Structural MRI guides surgical planning through the detection of tissue abnormalities, such as MTS or focal cortical dysplasia (Duncan et al., 2016). Focal cerebral metabolic abnormalities can be identified using PET and SPECT (Ganesan & Ursekar, 2014). Additionally, neuropsychological evaluation, functional magnetic resonance imaging (fMRI), Sodium Amytal (Wada) testing (Wada, 1949), electrical stimulation mapping, and other tools are useful in the presurgical evaluation of epilepsy. They may be used to help implicate cortical regions with distinct epilepsy syndromes or characteristics, map eloquent cortex, characterize baseline cognitive profiles, and lateralize language in surgical candidates, in order to avoid undesirable post-surgical cognitive outcomes (Baxendale, 2009; Benjamin et al., 2018; Hamberger & Cole, 2011; Loddenkemper & Staudt, 2011). Although such evaluations are intensive and time-consuming, the hope is that the data will converge on a single, well-defined EZ for surgical resection.

This ideal is not always met. In up to one-third of epilepsy surgical candidates, the data from the rigorous pre-surgical evaluation process do not conclusively localize an EZ, leading to recommendations for more invasive monitoring with intracranial EEG (King et al., 1997; Vakharia et al., 2018), including stereoelectroencephalography (Iida & Otsubo, 2017). Although these tools can be helpful in surgical planning in cases where the lesion apparent on MRI is incongruent with EZ localization found using scalp EEG (Pondal-Sordo et al., 2007), the placement of only a limited number of electrodes naturally leaves much of the cortex unexplored for definitively localizing the EZ. Besides, invasive EEG monitoring is expensive (requiring long-term hospital admission in order to implant the electrodes and capture spontaneous seizure activity within an epilepsy monitoring unit), invasive, and poses significant risks for

complications (Hamer et al., 2002; King et al., 1997; Önal et al., 2003). Due to discordant information from semiology, structural and functional neuroimaging, and neuropsychology, limitations of imaging resolution (Placantonakis et al., 2010; Wellmer et al., 2012), and potential overlap between the EZ with eloquent cortex, the ability to make decisions regarding the surgical treatment of epilepsy can be immensely restricted. The identification of sensitive, non-invasive, and cost-effective techniques for localizing the focus of epilepsy is critically needed to optimize the presurgical assessment of drug-resistant epilepsy, improve surgical outcomes, and increase the number of PWE for whom surgery is an option.

1.4 Neuropsychological Assessment

Neuropsychological assessment is a component in the presurgical evaluation of epilepsy. It characterizes individuals' cognitive strengths and weaknesses, can help to localize the EZ, and may in part predict post-surgical cognitive outcomes (Helmstaedter & Witt, 2012; Lezak et al., 2012). Presurgical neuropsychological assessment involves an examination of the cognitive and behavioural manifestations of neural changes in PWE, using comprehensive tests of intellectual, motor and sensory function. Cognitive tests tap domains including executive control, attention, visual-spatial abilities, language, and memory (Jones-Gotman et al., 2010; Lezak et al., 2012). Discrepancies between an individual's actual and expected performance on a given neuropsychological measure (estimated in relation to the same individual's performance on other tasks or their global intellectual functioning), unrelated to any secondary influences (i.e., medication effects, mood), may implicate dysfunction within particular brain regions. Where neuropsychology and all other evaluations agree on a single consistent EZ, the surgical team can be confident that a resection in this area would result in seizure freedom and minimal post-surgical cognitive deficits. Even in individuals with concordant data, chances of seizure relapse following surgery are generally about 30-40% (Engel, 1996; Engel, 2001; Téllez-Zenteno et al., 2005, 2010). A lack of concordance among measures, including neuropsychology, may prompt additional investigations to avoid missing the seizure focus and to prevent provoking detrimental post-surgical cognitive outcomes with surgery (Baxendale & Thompson, 2010).

Memory is a focus of neuropsychological assessment fundamental to the surgical work-up for temporal-lobe resection. In TLE, selective impairments in episodic memory capacity are apparent both prior to, and are most pronounced following, surgical treatment (Baxendale, 2008; Hermann et al., 1995; Lee et al., 2002; Sabsevitz et al., 2001; Spiers et al., 2001). Specific deficits in verbal memory tasks have traditionally been associated with a left temporal-lobe epileptic focus, whereas non-verbal memory deficits have been associated with a right temporal-lobe localization (Milner, 1972). More recently, however, a number of studies have demonstrated the relationships between nonverbal memory and right TLE, and verbal memory and left TLE, may be more inconsistent and unreliable than was once thought (Baxendale & Thompson, 2010; Bell & Davies, 1998; Glikmann-Johnston et al., 2008; Lee et al., 2002; McAndrews & Cohn, 2012; Saling, 2009). Still, it remains foundational in neuropsychological assessment to utilize simple, modality-specific (i.e., exclusively verbal or visual) stimuli to detect material-specific effects and to lateralize TLE (i.e., Jones-Gotman et al., 2010). As useful as they are, unimodal, or 'pure', tests of cognitive function are limited in their ecological validity and their ability to stimulate cognition in ways that might occur in the real world. Complex, multimodal, naturalistic stimuli (i.e., audiovisual clips) may be a valuable complement to the information obtained using traditional neuropsychological measures, more likely to approximate the demands of everyday cognition and capture aspects of cognition missed by simpler stimulus paradigms.

Localization of the EZ and eloquent cortex is further complicated where functional reorganization of the cortex has occurred. People with TLE are often affected by early onsetting, chronic cerebral insults, which alter typical neural development and organization. Functional reorganization in TLE is evidenced, for instance, by higher rates of atypical (right or bilateral) hemispheric dominance for language (Branch et al., 1964; Duchowny et al., 1996; Hamberger & Cole, 2011; Möddel et al., 2009; Rausch & Walsh, 1984; Springer et al., 1999) compared to the general population. Functional reorganization may serve to compensate for network dysfunction and cognitive impairment resulting from brain injury (Alessio et al., 2013; Bettus et al., 2009; Xu et al., 2014; Zhou et al., 2019). Still, the impacts of chronic, uncontrolled epileptic activity across broad functional networks put individuals with poorly controlled epilepsy at risk for cognitive decline over time (Hermann et al., 2006).

Given extensive neural reorganization is common in TLE, conventional presurgical neuropsychological evaluations may ultimately benefit from integration with functional network-oriented methods. Evidence from a recent study by Warren and colleagues (2017) supports this notion. Warren and colleagues (2017) tested the congruence between predicted and observed cognitive and behavioural outcomes in patients previously identified (in Warren et al., 2014) as having focal lesions in highly connected (hub) or less well-connected cortical areas. They found that the severity of neuropsychological deficits experienced by brain-lesioned patients often exceeded the predictions of clinical neuropsychologists when the lesion in question was a hub. It is necessary to continue to explore the efficacy of novel network-oriented tools in the presurgical evaluation of epilepsy.

1.5 Magnetic Resonance Imaging

The use of non-invasive methods of brain imaging, like MRI is an established part of presurgical assessment in epilepsy. MRI allows clinicians and researchers to capture detailed anatomical images of the brain, useful for identifying potential structural lesions underlying an epilepsy syndrome (Rosenow & Lüders, 2001). In MRI, a strong magnetic field (typically 1.5 or 3 Tesla [T]) is applied to the head, causing the hydrogen atoms abundant in the water and fat molecules that make up the human brain to become polarized. Oscillating pulses of radio waves excite the hydrogen atoms, causing them to spin out of equilibrium. When the radiofrequency pulses are turned off, the hydrogen atoms emit energy, detectable by MRI sensors, as they realign with the strong static magnetic field. Since tissues in the brain (grey matter, white matter, cerebrospinal fluid) are made up of different proportions of water and fat, they will vary in the time it takes for their hydrogen atoms to realign with the magnetic field and will emit different amounts of energy during the realignment process, creating contrast in the image.

Individuals with focal, as opposed to generalized, epilepsy are more likely to show visible structural lesions on MRI – the most common of which is MTS (Stafstrom & Carmant, 2015). At conventional MR field strengths (1.5 and 3T) structural lesions cannot be identified in about a fourth of TLE cases (Carne et al., 2004; Hong et al., 2002), likely reflecting the limitations of the spatial resolution of MRI (Kuba et al., 2011; Mueller et al., 2009; Palacios Bote

et al., 2008; Shah et al., 2019), resulting in greater uncertainty in localizing epileptogenic tissue. PWE with visible structural lesions on presurgical MRI tend to achieve greater seizure freedom than cases of non-lesional or 'MRI-negative' epilepsy (Téllez-Zenteno et al., 2010).

fMRI is a powerful, non-invasive tool used in some surgical centres to investigate the neural correlates of key cognitive functions (i.e., language and memory) so that they can be spared during surgical resection, and to predict postsurgical cognitive outcomes (Benjamin et al., 2018; Limotai & Mirsattari, 2012; McAndrews, 2014; McAndrews & Cohn, 2012). fMRI provides an indirect measure of brain activity as an individual performs cognitive tasks (or simply rests) within the scanner. Increased neural activity within a given brain region results in the increased recruitment of oxygenated blood, altering the local blood volume concentration of oxygenated relative to deoxygenated hemoglobin. As oxygenated and deoxygenated hemoglobin have distinct magnetic properties, changes in their relative proportions evoke a magnetic signal change that is recorded as the blood-oxygen-level-dependent (BOLD) signal (Kwong et al., 1992; Ogawa et al., 1992). fMRI is sensitive to the contrast between active and inactive cortical regions over time, and thus may be particularly useful for localizing the EZ in non-lesional focal epilepsies while individuals are engaged in a task or at rest (Duncan et al., 2016).

1.5.1 Resting-State fMRI

rs-fMRI captures intrinsic brain activity while subjects are at rest in the scanner. Early views of the brain as a purely reflexive machine, reactive to environmental demands (Sherrington, 1906) have long been disregarded in light of evidence of the brain's ongoing activation during relaxed non-task states (Raichle et al., 2001). rs-fMRI approaches have revealed various brain networks active in healthy subjects at rest, including structures involved in visual and auditory processing, motor function, memory, and the 'default mode' network (DMN; Biswal et al., 2010; Raichle et al., 2001; Smith et al., 2009). While not currently used routinely in the pre-surgical evaluation of epilepsy, studies employing rs-fMRI have contributed significantly to our understandings of functional networks in normal and pathological brains. For instance, investigations by McCormick and colleagues (2013, 2014) found reduced functional connectivity between the DMN and the affected hippocampus, and increased connectivity with the non-

affected contralateral hippocampus, to be associated with better presurgical memory ability and greater postsurgical memory decline (McCormick et al., 2013, 2014). The practical features of rs-fMRI, namely low performance demands and high tolerance in the absence of specialized stimuli or tasks, have made it particularly suitable for use with clinical populations (Greicius, 2008).

rs-fMRI has several drawbacks. The unconstrained nature of rs-fMRI promotes restlessness and head movement within the scanner, resulting in unreliable observations of the neural effects of interest (Lund et al., 2005) and posing a significant challenge for the interpretation and generalizability of results (Barnett et al., 2017; Tagliazucchi & Laufs, 2014; Van Dijk et al., 2012; Vanderwal et al., 2015). Head motion-related artefacts tend to be particularly prominent in data derived from investigations involving children, older adults and clinical populations (Greene et al., 2018; Huijbers et al., 2017; Vanderwal et al., 2015), and should be taken into consideration in studies of people with epilepsy (Lemieux et al., 2007).

Moreover, the lack of explicit task demands in rs-fMRI, in conjunction with the monotonous lull of earplug-dampened scanner noise, promotes dynamic alterations in levels of awareness and wakefulness in the scanner (Richter et al., 2005; Tagliazucchi & Laufs, 2014; Van Dijk et al., 2012; Vanderwal et al., 2015). An EEG-fMRI examination of wakefulness during resting-state scans found over half of individuals fell asleep during scanning (Tagliazucchi & Laufs, 2014). That variability in states of arousal may lead to unreliability in observations of functional connectivity. This is particularly concerning when it comes to examinations of individuals with disorders that cause changes in alertness and wakefulness, geriatric patients, individuals taking sedative or anti-epileptic medications, and sleep-deprived participants (Chaudhuri & Behan, 2004; Siniscalchi et al., 2013; Vanderwal et al., 2015). A meta-analysis and systematic review of fatigue in 700 adult patients with epilepsy found that the degree of fatigue was higher in epilepsy compared to the general population (as indicated most commonly by the Fatigue Severity Scale [FSS; Krupp et al., 1989]), with nearly 50% of patients with epilepsy reporting episodes of fatigue (Kwon et al., 2017). Variability in arousal may introduce unreliability and reduce the efficacy of techniques to examine functional networks in PWE.

Besides this, resting state essentially represents an unknown state of cognition. fMRI signals observed in different subjects at rest represent a combination of various cognitive states (i.e., spontaneous thought, visual or auditory mental imagery, somatosensory awareness) and spontaneous cerebral activity (Alexander Diaz et al., 2013; Leopold et al., 2003). Since resting-state data are derived in the absence of an explicit task, and each individual's neural activity is at the mercy of their wandering mind, the inferences and comparisons we can make to understand complex cognitive processes are limited. Thus, accurate quantification of the reliability of the BOLD signal undoubtedly suffers as the result of low behavioural constraint and a lack of a common stimulus in resting-state paradigms. Evaluating neural activity and cognitive processing in response to a stimulus that is dynamic and behaviourally unconstrained, yet consistent across individuals, may be ideal for addressing the limitations inherent to rs-fMRI.

1.5.2 Task-Based fMRI

Task-based fMRI paradigms capture brain activity by engaging individuals in a cognitive task. In contrast to rs-fMRI, task-based fMRI paradigms generally employ highly controlled, perceptually abstracted, idealized, simplified, artificial, or static stimuli in clearly defined blocks, and often rely upon hypothesis-driven data analyses (i.e., based on general linear models defined *a priori*) to elucidate segregated cortical function. Tasks of verbal fluency (generating words that start with a given letter), responsive naming (generating a word given a verbal description of its meaning), or semantic decision-making (deciding whether a given word meets certain semantic criteria) are commonly presented in fMRI for lateralizing language abilities in PWE before surgery (Benjamin et al., 2018; Silva et al., 2018). This is done by contrasting BOLD activation between the two hemispheres while an individual is engaged in a language-related task, compared to a baseline (McAndrews & Cohn, 2012). Task-based fMRI paradigms are also used to identify hemispheric differences in material-specific memory abilities (Cano-López et al., 2018; Szaflarski et al., 2017). Task-based fMRI data are often interpreted using cognitive subtraction, which assumes that differences in brain images acquired during a task condition and a control condition reflect activation due to the process of interest. However, the assumption of pure insertion, which is implicit in cognitive subtraction, has been criticized as an overly

restrictive representation of neuronal recruitment during cognitive processes (see Friston et al., 1996).

Good concordance has been observed between task-based fMRI protocols and 'gold-standard' tools for language lateralization (i.e., Wada testing), with the added advantage being that fMRI is non-invasive (Detre et al., 1998; Golby et al., 2002; Janecek et al., 2013; Szaflarski et al., 2008). Moreover, task-based fMRI paradigms have been useful in predicting cognitive decline after surgery for TLE (Binder et al., 2008; Powell et al., 2008; Rabin et al., 2004). For instance, Binder and colleagues (2008) found that preoperative fMRI predicted verbal memory decline following surgery for TLE, above other non-invasive measures including preoperative test performance and medical history data. Rabin and colleagues (2004) found that hemispheric asymmetries in mesial temporal lobe activation detected with fMRI correlated significantly with memory asymmetries determined with invasive Wada testing and memory performance following temporal lobectomy for TLE.

Task-based fMRI also has disadvantages. Traditional paradigms lack the spatial and temporal complexity that characterize real life. Experimental fMRI protocols provide insight into distinct cognitive constructs by presenting brief (i.e., less than 500 ms) and basic (i.e., Gabor patches or pure tones) stimuli to engage only a subset of specialized functional regions within the brain. In this sense, results ascribed to segregated brain regions are favoured by task-based fMRI (Büchel & Friston, 1997; Downing et al., 2001; Friston & Büchel, 2000; Malach et al., 1995; Zeki, 1991). Hasson and colleagues (2004) posited that natural vision bears little resemblance to vision in a highly controlled task paradigm. A natural viewing experience involves unconstrained eye movements across complex non-stationary multi-object scenes and the integration of both external sensory information and internal information from context and emotional valence (Hasson et al., 2004). Further, in natural environments, viewers are engaged in the moment, are in sympathy with others, and anticipate upcoming developments. Accordingly, natural cognition and action unfold over relatively long time scales and require the simultaneous and interdependent recruitment of brain-wide networks, highlighting the limited ecological validity of specialized task-based fMRI paradigms (Chaytor & Schmitter-Edgecombe, 2003; Hasson et al., 2008b). Further, task-based fMRI paradigms sometimes require long scans of multiple runs

to obtain reliable data, and thus may not be ideal for use with clinical samples. An accurate understanding of the functional capacity of the whole-brain during daily cognitive processes therefore requires the use of paradigms simulating real-world conditions.

1.6 Naturalistic Stimulation in fMRI

A growing trend in neuroscience has been to use movies, television shows, video games, music, virtual reality or audiobooks to study the human brain in more ecologically valid and naturalistic settings. So-called naturalistic stimulation has been a focus of numerous fMRI investigations of humans (Bartels & Zeki, 2004a, 2004b, 2005; Bartels et al., 2008; Betti et al., 2013; Golland et al., 2007; Hasson et al., 2004, 2008c, 2009; Hasson & Honey, 2012; Haxby et al., 2001; Lahnakoski et al., 2012b; Maguire, 2012; Malinen et al. , 2007; Mobbs et al., 2006; Rao et al., 2007; Wilson et al., 2008; Zacks et al., 2001). The proliferation and refinement of non-invasive neuroimaging methodologies and associated data analytic techniques make it possible to examine normal and pathological brain function under conditions approximating real life. Appealingly, naturalistic stimulation in fMRI affords several advantages over traditional resting-state and task-based paradigms, useful for exploring brain function and sensitively characterizing neural abnormalities in clinical populations (see Eickhoff et al., 2020 for summary).

Naturalistic stimuli, like real world encounters, require the integration of multiple sensory inputs and the involvement of attentional, perceptual, emotional, cognitive, and language-related functional networks for the duration of the stimulus (Hasson et al., 2008b). Given their ability to depict natural scenes in two dimensions, engaging movie or television clips are the most used naturalistic stimuli. Naturalistic neuroimaging paradigms are useful in contributing to our understanding of brain connectomics (Wang et al., 2017), as are resting-state paradigms (Biswal et al., 2010; Preti et al., 2017), although under natural, stimulus-driven conditions. Placing ecologically relevant constraints on neuronal processes effectively allows for the selective engagement of broad brain networks (Bartels & Zeki, 2004a; Hasson et al., 2004; Jääskeläinen et al., 2008; Lee et al., 2013; Lerner et al., 2011). Moreover, naturalistic stimulation in fMRI enables measurement of stimulus-evoked responses corresponding to perceptual and higher-

order aspects of a stimulus. The increased ecological validity of naturalistic stimulation in fMRI provides a means for addressing complex research questions which cannot be examined with unfocused resting-state nor overly controlled task-based paradigms (i.e., questions concerning natural vision, temporal scales of processing, memory, social and affective symptoms of patients with psychiatric disorders, or the neural basis of inter-group differences in such areas as theory of mind, verbal communication, prediction, event segmentation, and narrative comprehension; Adolphs et al., 2016; Hasson & Honey, 2012; Hasson et al., 2010; Klin et al., 2002; Zaki & Ochsner, 2009). Ultimately, a major advantage of naturalistic fMRI paradigms is that they allow us to make better inferences about functional networks in response to dynamic stimuli that more closely resemble real life. Such paradigms may be valuable for exploring multi-modal functional relationships in the pathological brains of PWE.

Because engaging with a movie or audio clip in the scanner is simple and enjoyable, this paradigm can be used effectively with clinical populations. In particular, naturalistic fMRI paradigms may be useful for collecting data from those who have trouble limiting motion or staying awake during scanning, who feel anxious or discouraged performing difficult or repetitive tasks in the scanner, or who are generally nervous about being in the scanner (Eickhoff et al., 2020; Wang et al., 2017). Engaging with an attentionally captivating naturalistic stimulus within the scanner reduces subject boredom, movement, and sleepiness, compared with resting-state paradigms, ultimately improving data quality.

An additional benefit of naturalistic paradigms in fMRI is that, despite their seemingly uncontrolled nature, dynamic and complex naturalistic stimuli may reveal more reliable, functionally selective and time-locked responses than are detectable using conventional resting-state or task-based paradigms (Golland et al., 2007; Hanson et al., 2009; Hasson et al., 2004, 2008a, 2008c 2010; Jääskeläinen et al., 2008; Wilson et al., 2008). Electrophysiological studies demonstrate increased visual cortical response reliability within subjects with repeated presentations of movie clips (Belitski et al., 2008; Mechler et al., 1998). Similarly, an fMRI study by Wang and colleagues (2017) examined the test-retest reliability of functional connectivity networks in a naturalistic fMRI paradigm compared to resting-state, over a period of three months. They rated the within-subject test-retest reliability as ‘good to excellent’ during

their natural viewing condition, improved on average by 50% across various connectivity measures when compared to resting-state. This improvement in reliability was observed not only in sensory (audio-visual) networks, but also in higher-order default mode and attentional networks and was suggested to be robust to the preprocessing approach, thresholding strategy, and parcellation scheme (Wang et al., 2017). Moreover, test-retest reliability appeared to improve throughout the naturalistic viewing paradigm, which Wang and colleagues (2017) interpreted as reflecting increased cognitive engagement as the storyline developed. The superior reliability of naturalistic over task-free resting-state conditions has also been demonstrated through improved accuracies of test-retest matching algorithms used to identify subjects based on their individual functional connectivity patterns (Vanderwal et al., 2015). Furthermore, demonstrations comparing the evoked BOLD fMRI response time courses across different subjects (Hasson et al., 2004) or within the same subject by repeated presentations of the same stimulus (Golland et al., 2007; Hasson et al., 2008c), revealed naturalistic conditions elicit highly reliable neuronal responses across widespread cortical regions (Golland et al., 2007; Hasson et al., 2004, 2008a, 2008c; Jääskeläinen et al., 2008; Wilson et al., 2008).

Although widespread, responses during naturalistic stimulation have been observed to be functionally selective, in that they differ from one brain area to another (Hasson et al., 2010). For example, while activity in a given temporal lobe region (i.e., A1+) may be positively correlated with activity in temporal and frontal areas and negatively correlated with activity in occipital and parietal areas, activity in a given frontal lobe region (i.e., dlPFC) may show negative correlations with activity in temporal regions and positive correlations with activity in occipital and parietal regions. Response time courses across individuals have also been demonstrated to be time-locked to the content of the presented naturalistic stimulus (Hasson et al., 2004; Hasson et al., 2008c). The ability of naturalistic stimulation paradigms to induce reliable, functionally selective and time-locked responses may prove useful in assessments of individuals in clinical samples, where the goal may be to maximize the sensitivity to individual differences in neural processing.

1.7 Inter-Subject Correlation

Movie viewing is an engaging, continuous task that yields data lending itself to recently introduced unbiased, data-driven analytic strategies, like inter-subject correlation (ISC). Originally introduced by Hasson and colleagues (2004), ISC is a conceptually simple, model-free approach for quantifying similarity in the spatiotemporal patterns of fMRI activity across human subjects (Bartels & Zeki, 2004a; Hasson et al., 2004; Hejnar et al., 2007) , and even across species (Mantini et al., 2012). ISC analyses summarize the degree of neural synchronization during the experiment based on timeseries correlation between corresponding voxels or regions in two subjects, where higher correlations are typically interpreted as synchronous activations. Increased variability in brain activity across individuals experiencing a common stimulus (low ISC) has been thought to reflect either a less engaged state of information processing (as in daydreaming) or a highly engaged, although idiosyncratic state of processing (Hasson et al., 2008b, 2009). Such asynchronous responding relates to poor comprehension of (Hasson et al., 2009) and memory for (Hasson et al., 2008a) the stimulus.

A major advantage of ISC for the analysis of fMRI data from naturalistic stimulation is its ability to identify neural activation patterns without the need for *a priori* stimulus time-course models specific to particular brain regions (Pajula et al., 2012). Besides this, ISC quantifies and compares neural response patterns over the time course of a stimulus, rather than comparing mean response amplitudes to a pre-determined baseline (as in general linear model-based analyses). Thus, inferences about neural activation in different brain areas are based solely on the similarities in hemodynamic responses across subjects engaged with the same stimulus (Pajula et al., 2012). ISC is also superior to traditional analytic methods in that correlations computed across subjects are less susceptible to idiosyncratic physiological noise and head motion compared to correlations computed across voxels within a subject (Simony et al., 2016).

Studies of fMRI while neurologically normal individuals watch an engaging movie have been particularly popular, and reveal highly reliable ISC elicited in widespread sensory, cognitive, attention, and emotion-related neural networks (Anderson et al., 2013; Bartels & Zeki, 2005; Byrge et al., 2015; Finn et al., 2018; Golland et al., 2007; Hanson et al., 2009; Hasson et

al., 2004, 2008a, 2008c, 2009; Hasson & Honey, 2012; Jääskeläinen et al., 2008; Kauppi et al., 2010b; Lahnakoski et al., 2014; Malinen et al., 2007; Naci et al., 2014; Nummenmaa et al., 2012; Salmi et al., 2013; Wilson et al., 2008). Hasson and colleagues (2008b) observed highly synchronous, statistically significant cortical activity in up to 65% of the neocortex, depending on the movie stimulus used (the same Hitchcock clip that we used elicited the highest levels of synchronization across viewers). The topography of ISC patterns appears to depend on the properties of the stimulus, with movie scenes rated as most engaging eliciting the highest degree of neural synchronization (Dmochowski et al., 2014; Naci et al., 2014). Likewise, neural synchronization had been observed to be reduced with disruptions to the story narrative (Dmochowski et al., 2014; Hasson et al., 2008c; Naci et al., 2014). Further, 'reverse correlation' methods have found that peak regionally specific cortical responses corresponded with emotionally charged scenes and particular aspects of the film (Hasson et al., 2004). Overall, studies of movie-driven fMRI reveal a tendency for the brains of neurotypical individuals to 'tick together', or to stereotypically respond, during free viewing of a complex stimulus.

Engaging movies and narratives draw viewers/listeners into a shared experience. ISC investigations have provided insight into inter-group differences in neural synchronization and have been previously applied to a wide variety of fMRI experiments, involving movies (Golland et al., 2007; Hasson et al., 2004, 2008a, 2008b; Kauppi et al., 2010b; Nummenmaa et al., 2012), news reports and educational television shows (Cantlon & Li, 2013; Schmälzle et al., 2013), music (Abrams et al., 2013; Trost et al., 2014), aesthetic performances (Herbec et al., 2015; Jola et al., 2013), and political speeches (Schmälzle et al., 2015). ISC has been used to explore shared processing of emotional stimuli (Nummenmaa et al., 2012) and language (Honey et al., 2012), as well as to probe social cognition, memory, and learning (Furman et al., 2007; Golland et al., 2007; Hasson et al., 2004, 2008a, 2008c; Wilson et al., 2008). Besides fMRI, ISC has been applied to data derived in other neuroimaging modalities, including extracranial EEG (Bridwell et al., 2015), and intracranial EEG (Potes et al., 2014).

ISC methodology has also been used to detect deviations in neural synchronization among various clinical groups in comparison to healthy subjects, serving as a unique non-invasive functional biomarker for abnormalities in brain function (Hasson et al., 2010). Studies

using ISC analyses in individuals with Autism Spectrum Disorder have found regional temporal synchronization of fMRI signals evoked during free viewing to be less synchronized both within the clinical group and with neurotypical controls, suggesting people with autism respond in more individualistic ways to naturalistic stimulation than controls (Byrge et al., 2015; Hasson et al., 2009; Salmi et al., 2013). Similar results emerged in an examination of inter-subject correlation evoked by the viewing of cartoon video clips in individuals with Down Syndrome, compared with healthy controls (Anderson et al., 2013). In a study by Finn and colleagues (2018), participants with high and low trait-level paranoia listened to an original narrative describing an ambiguous social scenario during fMRI scanning. Their results showed that the brains of individuals with high levels of trait paranoia were highly synchronized, particularly in theory-of-mind regions, during narrative engagement (Finn et al., 2018). Hyett and colleagues (2015) observed that participants with clinical depression exhibited weakened ISC in the right frontoparietal attention network while watching a negatively emotional film. Rikandi and colleagues (2017) found that abnormal precuneus activity during naturalistic information processing in persons with first-episode psychosis related to the processing of fantasy and severity of positive psychotic symptoms. Older people also appear to respond more variably and idiosyncratically during movie watching (Campbell et al., 2015). I was inspired, by the proliferation of research using naturalistic stimulation in conjunction with ISC, to explore neural synchronization in PWE.

1.8 Preprocessing of fMRI Data

Preprocessing is necessary to clean and standardize fMRI data prior to statistical analysis. The goal of preprocessing is to minimize sources of false positive errors (i.e., misinterpreting head motion-induced noise as activation) without introducing excessive false negative errors to the data (Esteban et al., 2019). Extracting signal reflecting true neural activity is key for ensuring the validity and interpretability of results (Ashburner, 2009). Preprocessing generally involves a) co-registering brains to a standard space (spatial normalization) to minimize variability in signal localization across individuals (Crinion et al., 2007), b) spatiotemporal filtering to balance resolution, signal sensitivity, and anatomical correspondence across images (Mikl et al., 2008; Pajula & Tohka, 2014), and c) identifying and reducing the effects of nuisance sources and

imaging artifacts on the data (through slice-timing, head-motion, and susceptibility distortion corrections, etc.; Caballero-Gaudes & Reynolds, 2017; Lindquist, 2008; Sladky et al., 2011). As preprocessing involves numerous steps, researchers and clinicians often rely on robust processing pipelines, like fMRIPrep (Esteban et al., 2019), to conveniently prepare fMRI data for analysis.

A number of strategies have been developed to mitigate the impact of motion-related artefacts on the fMRI signal. Methods including regressing motion-related covariates from volume-realignment parameters ('nuisance regression') or deleting ('scrubbing') or regressing out ('spike regression') high-motion volumes from the fMRI time-series have limitations (Lemieux et al., 2007; Power et al., 2012; Satterthwaite et al., 2013; Yan et al., 2013a). These strategies remove motion-induced signal variations at the cost of also removing relevant signals or frequencies of interest, since global signals of motion comprise both signal and noise components (Satterthwaite et al., 2013; Yan et al., 2013a). Removal of global noise may ultimately introduce alterations in the connectivity structure of functional MRI data (Murphy et al., 2009; Weissenbacher et al., 2009; Yan et al., 2013b). Secondly, volume removal or regression with denoising results in a high and variable loss of temporal degrees of freedom (Yan et al., 2013a; Power et al., 2012). Reduced temporal degrees of freedom can be associated with substantial losses in statistical power and increased error variance between subjects (Yan et al., 2013b). A final limitation of such denoising procedures is the destruction of the autocorrelation structure of the fMRI time-series, preventing frequency filtering of fMRI data and distorting group differences in functional connectivity analyses (Yan et al., 2013a; Carp, 2013).

Alternate strategies aimed at identifying and removing motion-induced signal variations from fMRI data using Independent Component Analysis (ICA; Bell & Sejnowski, 1995; Comon, 1994) may overcome these drawbacks. ICA is computational method for decomposing data into spatially independent component maps (ICs) and their associated time courses (Beckmann et al., 2005; Beckmann & Smith, 2004; McKeown et al., 1998). Thus, ICA can be used to reliably separate neural signal from different sources of noise (i.e., motion-related, physiological, or scanner-induced noise), in a data-driven manner (Beckmann, 2012; Beckmann et al., 2005; Kelly et al., 2010; McKeown et al., 1998; Thomas et al., 2002). ICA-based denoising procedures

typically require re-training of a classifier for each new dataset and the manual labelling of ICA-derived components (i.e., ICA-FIX; Salimi-Khorshidi et al., 2014). While manual component classification is considered 'gold standard', it is a time-consuming and subjective process.

Recently, a number of attempts have been made to automate the classification of ICA-derived noise components (Bhaganagarapu et al., 2013; De Martino et al., 2007; Kochiyama et al., 2005; Kundu et al., 2012; Perlbarg et al., 2007; Pruim et al., 2015a; Rummel et al., 2013; Salimi-Khorshidi et al., 2014; Storti et al., 2013; Thomas et al., 2002; Tohka et al., 2008). ICA-based Automatic Removal of Motion Artefacts (ICA-AROMA) is an example of such an attempt (Pruim et al., 2015a, 2015b). ICA-AROMA aims to automatically identify and remove participant-specific head-movement-related components from functional data using robust temporal (high frequency content and maximum correlation with realignment parameters) and spatial (edge fraction and cerebrospinal fluid fraction) features. These features are defined *a priori* and are theoretically derived based on characteristics typically evaluated during manual denoising. Accordingly, ICA-AROMA does not require classifier re-training across datasets, pragmatically benefitting large-scale multi-site studies. Within a typical single subject preprocessing stream, ICA-AROMA is applied after spatial smoothing but before high-pass filtering and further nuisance regression.

Validation of ICA-AROMA confirmed its robustness, generalizability, and reproducibility in terms of its ability to remove motion artefacts, preserve the signal of interest, and prevent a loss in temporal degrees of freedom, in resting-state and task-based fMRI data. (Pruim et al., 2015a, 2015b). ICA-AROMA also largely preserves the autocorrelation structure of the fMRI time-series, increasing sensitivity to group-level activation (Pruim et al., 2015a, 2015b). ICA-AROMA is an optional component of the fMRIprep preprocessing pipeline (Esteban et al., 2019), making it widely accessible and easily applicable to new fMRI study data. Thus far, the employment of ICA-AROMA in investigations involving populations of clinical interest has been limited to resting-state derived functional data (i.e., Klaassens et al., 2017; Parkes et al., 2018; van Timmeren et al., 2018). To establish the utility of naturalistic fMRI paradigms for use with clinical populations, more research is needed to evaluate such paradigms in conjunction with commonly used strategies for removing motion-induced signal variation

from fMRI data. We wondered if denoising with ICA-AROMA without re-training a classifier on a set of naturalistic study data could potentially result in the removal of relevant components of the BOLD signal in addition to noise components. The result would be apparent reduced neural synchronization between subjects watching the same movie. For clinical applications, we would hope to ensure the BOLD signal is optimally preserved, so that we may have room to sensitively identify functional abnormalities in patients. To our knowledge, no study has examined the utility of ICA-AROMA for removing artefact from fMRI data derived using a naturalistic paradigm, where ISC can serve as a proxy for sensitivity.

1.9 Cortical Maps

For decades, neuroscientists have strived to subdivide the human brain into anatomically and functionally meaningful sections, to better understand how the brain works. The creation of cortical maps, or 'parcellations' has been one method of subdividing the brain based on areas that differ in their structural architecture, functional specialization and connectivity, and topographic organization. Maps of the brain's major cortical areas are advantageous for streamlining communication amongst researchers, allowing for comparisons of results between studies, and reducing data complexity and computational load while also enhancing statistical sensitivity and power in neuroimaging analyses (Glasser et al., 2016).

One example of a cortical map is the Glasser Parcellation (Glasser et al., 2016). The Glasser Parcellation was created using data from the Human Connectome Project (HCP; Van Essen et al., 2013) and an objective multi-modal semi-automated neuroanatomical approach. In this approach, two neuroanatomists interpreted and documented the properties of areal borders delineated by an algorithm informed by the spatial gradient magnitude of areal feature maps (rather than relying on evidence from post-mortem histological results, as in previous approaches). This method allowed for examinations of the correspondence in a large group of individuals (and a large replication sample) between measures of cortical thickness, myelin concentration, functional connectivity, and functional profile across tasks used in the HCP. The resulting Glasser Parcellation is a surface-based atlas that divides the brain's hemispheres each into 180 cortical regions, which can be grouped into 22 sections that can be distinguished based

on properties including geographic location and functional specialization (44 functional sections; Glasser et al., 2016; see Appendix A). The use of a parcellation scheme, like the Glasser Parcellation (Glasser et al., 2016), may be advantageous for examinations of ISC, as we might expect patterns of neural synchronization to vary in response to naturalistic stimulation at the level of functionally homogenous cortical areas.

1.10 Rationale

This work will explore the use of naturalistic stimulation in a sample of people with drug-resistant TLE, compared to a demographically matched group of healthy control participants. People watch a highly engaging film clip during functional MRI. Inter-subject correlation analysis is then used to compare patterns of neural synchronization during movie viewing between PWE and demographically matched neurotypical controls, at whole-brain and regional levels. It is expected that PWE will exhibit broad abnormalities of neural synchronization compared to controls during free-viewing of a movie stimulus, given the structural and functional pathology associated with prolonged epileptic activity. Moreover, this is the first ever investigation of the effects of an automated Independent Components Analysis-based denoising strategy (ICA-AROMA; Pruim et al., 2015b) on the temporal characteristics of movie-driven fMRI data derived in a clinical sample. The promise of this study is the potential for measures from naturalistic fMRI to serve as sensitive, non-invasive, and cost-effective biomarkers for clinical use in the assessment of epilepsy. A second aim of this work is to identify appropriate strategies for removing motion-induced signal variation from fMRI data derived using naturalistic stimulation (aka denoising) that maximize sensitivity and thus clinical utility.

Chapter 2

2 Methods

2.1 Participants

Presurgical epilepsy patients and demographically matched healthy controls were recruited as part of a large province-wide initiative (Eplink) funded and coordinated by the Ontario Brain Institute. Prior to participation, patient medical charts were reviewed to retrieve neuropsychological and pathology reports useful in identifying and classifying a patient's epilepsy. This classification was done by clinical personnel including neuropsychologists, neurologists, and neuropathologists, and is based on a variety of features, such as age at onset and duration of epilepsy, seizure classification, seizure etiology, syndromes by age of onset, medication history, clinical reports of pathology based on extracranial (and sometimes intracranial) EEG, 1.5T MRI, PET, and histologic findings.

Twenty-four persons presumed to have drug-resistant focal epilepsy and undergoing evaluation for resective surgery were recruited from the Adult Epilepsy Service, London Health Sciences Centre, London, ON, to participate in this study. Five of these were excluded following data acquisition due to audiovisual malfunction during the fMRI scan, and one was excluded due to issues of realignment, thus resulting in 18 PWE in the final analysis. All patients had at least basic proficiency in English and no record of significant developmental delay, history of major neurological comorbidities, psychiatric conditions, vision or hearing impairment, or other characteristics that would make it impossible to complete the study procedures. Twenty-four neurologically healthy controls (HC) were recruited from the London community and were approximately matched to PWE on age (Welch's t-test, $p = .997$), years of education (Welch's t-test, $p = .104$), and sex distribution (Chi-squared test, $p = .212$). All control participants had basic proficiency in English and reported no history of psychiatric illness, neurological disorder, vision or hearing impairment. All participants provided informed consent, and ethical approval was obtained from the Health Sciences Research Ethics Board of the University of Western Ontario and Lawson Health Research Institute (See Appendix B).

2.2 Procedure

As part of the broader Eplink protocol, all participants provided demographic information pertaining to their age, month and year of birth, sex, handedness, ethnicity, level of education, marital status, employment status, and household income (optional). Participants also completed a review of medical history and provided a list of their current medications. Epilepsy patients completed clinical neuropsychological evaluation, clinical EEG monitoring, genomic evaluation, seizure diaries and a series of questionnaires related to quality of life (The World Health Organization Quality of Life [WHOQOL-BREF]; WHOQOL Group, 1998), psychiatric symptomatology (The Brief Symptom Inventory [BSI] and the Patient Weighted Quality of Life in Epilepsy [QOLIE-31-P]; Cramer & Van Hammée, 2003; Derogatis & Melisaratos, 1983), depression (The Quick Inventory of Depressive Symptoms-Self-report [QIDS-SR]; Rush et al., 2003), anxiety (The Generalized Anxiety Disorder Scale [GAD-7]; Spitzer et al., 2006), sleep quality (The Pittsburgh Sleep Quality Index [PSQI]; Buysse et al., 1989), stigma (The Epilepsy Stigma Scale; DiIorio et al., 2003), and disability (The Sheehan Disability Scale; Leon et al., 1997). Healthy controls completed a similar set of questionnaires related to quality of life (WHOQOL-BREF), psychiatric symptomatology (BSI), depression (QIDS-SR), anxiety (GAD-7) and sleep disturbances (PSQI). Participants who endorsed any degree of suicidal ideation on the QIDS-SR were further followed up using the Columbia-Suicide Severity Rating Scale Screener Recent (C-SSRS; Posner et al., 2011). For the purposes of this project, I will only present a subset of these data. Specifically, I include items pertaining to participant demographics, epilepsy characteristics, and full-scale intelligence quotient (FSIQ) as assessed by the Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler, 2011) or the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008) on clinical neuropsychological evaluation (Table 2-1).

Table 2-1: Participant Characteristics.

	HC	PWE
n	24	18
Sex (F:M)	14:10	7:11
Age (range; *M* ± *SD*)	17-61; 35.63 ± 14.89	18-59; 35.61 ± 12.96
Years of education (*M* ± *SD*)	16.43 ± 2.04	14.94 ± 3.30
Handedness (R: L)	19:5	17:1
Seizure lateralization (R: L: BL)	.	7:9:2
Seizure localization	.	14 temporal; 1 frontal-temporal; 3 temporal + insular
Evidence of MTS on MRI	.	11 probable; 7 none
Age at epilepsy onset (*M* ± *SD*)	.	17.78 ± 13.72
Years since onset (*M* ± *SD*)	.	17.83 ± 16.80
FSIQ (*M* ± *SD*)	.	96.06 ± 15.77

Note. HC = healthy controls, demographically matched to epilepsy sample; PWE = sample of people with epilepsy; F = female; M = male; L = left; R = right; BL = bilateral; MTS = mesial temporal sclerosis; MRI = magnetic resonance imaging; FSIQ = full-scale intelligence quotient.

2.3 Relevant Image Acquisitions

Participants underwent MRI at Robarts Research Institute as part of the Eplink protocol. Volume acquisitions for healthy controls and PWE consisted of T1-weighted structural MRI, T2-weighted fluid attenuation inversion recovery (FLAIR), diffusion tensor imaging (DTI), and fMRI. fMRI consisted of 2 runs, including 6 min 33 s of resting-state imaging (with eyes closed), followed by 8 min during which participants watched an audiovisual movie clip projected on a mirror box in the scanner. The acquisitions of interest for the present study were the T1-weighted structural scans for image registration and localization and the functional (T2*; movie-driven) scans, which are described in more detail below.

Whole-brain imaging was performed on a 3T Siemens Magnetom Prisma scanner (Siemens Healthcare, Erlangen, Germany) with a standard 32-channel head coil. A T1-weighted anatomical image was obtained at the start of scanning using a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (Repetition time [TR] = 2200 ms, echo time [TE] = 2.98 ms, flip angle [FA] = 9˚, acquisition time [TA] = 5 min 21 s, inversion time

[TI] = 900 ms, voxel size = 1 × 1 × 1 mm, field of view [FOV]= 256 mm^2, 176 × 256 × 256 matrix). T2*-weighted functional scans were acquired using a gradient echo (GRE) echo-planar imaging sequence (TR = 2000 ms, TE = 30 ms, FA = 75˚, 33 slices, voxel size = 3 × 3 × 3 mm, FOV = 192 mm^2, 64 × 64 matrix, 25% interslice gap collected in interleaved descending order). The movie run comprised 246 scans.

The film clip used was a short, black-and-white, suspenseful 8 min clip sampled from the 1961'Alfred Hitchcock Presents' television episode entitled 'Bang! You're Dead', that had been edited to maintain the narrative structure of the original 22 min episode. This clip depicts a boy playing with a real gun that he believes to be a toy and has several moments of heightened suspense to engage the audience, but it ends positively and is not thought to be excessively distressing for the viewer. Previously used in a number of fMRI studies (Ben-Yakov & Henson, 2018; Campbell et al., 2015; Geerligs et al., 2015; Hasson et al., 2004, 2008b 2010; Naci et al., 2014; Shafto et al., 2014; Taylor et al., 2017), this clip has been shown to reliably elicit widespread synchronous activity across participants in widespread regions of the cortex (Hasson et al., 2004, 2008b 2010) and its suspenseful plot has been shown to promote engagement with the clip (Naci et al., 2014). Because it was originally broadcast in 1961, and is not regularly rebroadcast, it is currently obscure and therefore has the advantage of being novel to most participants, further promoting engagement with and interest in the clip.

During the 8 min suspenseful movie clip, participants were instructed to pay attention and follow the plot of the movie as they would if they were watching any other movie or television show. The movie stimulus was presented using the Psychophysics toolbox (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) in MATLAB2014b (Mathworks, Natick, MA, USA), projected on a screen behind the MRI bore, and reflected via a mirror mounted on the head coil. Participants were provided with MR-compatible headphones (Sensimetrics, S14; www.sens.com) for sound delivery and, when necessary, MR-compatible lenses to correct vision. Foam padding was used to restrict head motion. A sound-check was performed prior to scanning, consisting of a short sound clip containing some music and conversation, to ensure that the volume was comfortable and that participants could hear well in both ears. The sound level was then adjusted depending on whether participants found the volume too loud. Participants

were offered a squeeze ball which stops scanning and were encouraged to use it if needed. Participants were instructed over a two-way intercom between scans.

Following the scan, all participants completed a memory test based on the content of the film clip presented in the scanner, which included familiarity, timeline and comprehension judgement questions (Ladowski, 2019). Participants also completed several standardized neuropsychological assessments of learning and memory as part of the Eplink protocol. 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), the Rey Auditory Verbal Learning Test (RAVLT; Strauss et al., 2006), and the Conditional Associative Learning Test (CALT; Petrides, 1985). The CALT is a measure of spatial memory and learning. The RVDLT is a measure of visual memory and delayed recall. The RAVLT is a measure of auditory memory and delayed recall. The Names and Doors subtests are measures of verbal and visual recognition. Healthy controls additionally completed the Matrix Reasoning and Vocabulary subtests of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler, 2008) as measures of nonverbal/fluid intelligence and crystallized intelligence, respectively. Post-scan testing took approximately 1 hr 20 min.

2.4 Image Preprocessing

Results included in this document come from preprocessing performed using fMRIPrep 1.3.2 (Esteban et al., 2019, 2020), which is based on Nipype 1.1.9 (Gorgolewski et al., 2011, 2017; see Appendix C for full pipeline details).

2.5 Image Post-Processing

Following preprocessing with fMRIPrep, we ran a Snakemake (Köster & Rahmann, 2012) workflow as a Brain Imaging Data Structure (BIDS; v1.4.0) App to denoise the movie data (Khan, 2020; http://github.com/akhanf/denoise-fmri). This denoising pipeline operated on the preprocessed BOLD images in MNI space outputted by fMRIPrep. One set of movie data was smoothed with a Gaussian kernel of 10 mm full width at half maximum (FWHM) and voxel-

wise denoising using a general linear model was performed, which included 6 realignment parameters, cerebrospinal fluid (csf), and white matter (wm), using the noise-regressors generated by fMRIPrep. A second set of movie data was additionally denoised with ICA-AROMA (Pruim et al., 2015b) following smoothing with a Gaussian kernel of 10 mm FWHM and but prior to voxel-wise denoising with 6 realignment parameters, csf, and wm. This was done 'non-aggressively', meaning that the variance specifically assigned to identified noise, but not signal, components was removed.

The resulting (AROMA and non-AROMA) denoised movie-driven volumetric data were then resampled to the brain's cortical surface. First, we used a Snakemake workflow (Khan, https://github.com/khanlab-snakemake/hcp_mmp_to_native) to generate native-space Human Connectome Project multi-modal parcellation (HCP mmp) segmentations (Glasser et al., 2016). This workflow required subjects' structural MRI data reconstructed and anatomically segmented with FreeSurfer (v7.1; http://surfer.nmr.mgh.harvard.edu/; see Appendix D for detailed procedure). Second, the data was mapped and resampled to these segmentations in HCP's symmetric fsLR (Van Essen et al., 2011) space which contains a predefined number of surface vertices, allowing vertex to vertex comparisons across subjects, using several Connectome Workbench commands (v1.4.2; Marcus et al., 2011; Van Essen et al., 2001).

2.6 Parcellation

The Glasser parcellation (Glasser et al., 2016; Figure 2-1) was then applied to the data in surface space. The Glasser parcellation is a surface-based map of the brain's major cortical areas that divides each hemisphere into 180 cortical regions (360 parcellated regions), which can then be grouped into 22 distinct sections based on common properties including geographic proximity and functional similarity (44 parcellated functional sections; Glasser et al., 2016).

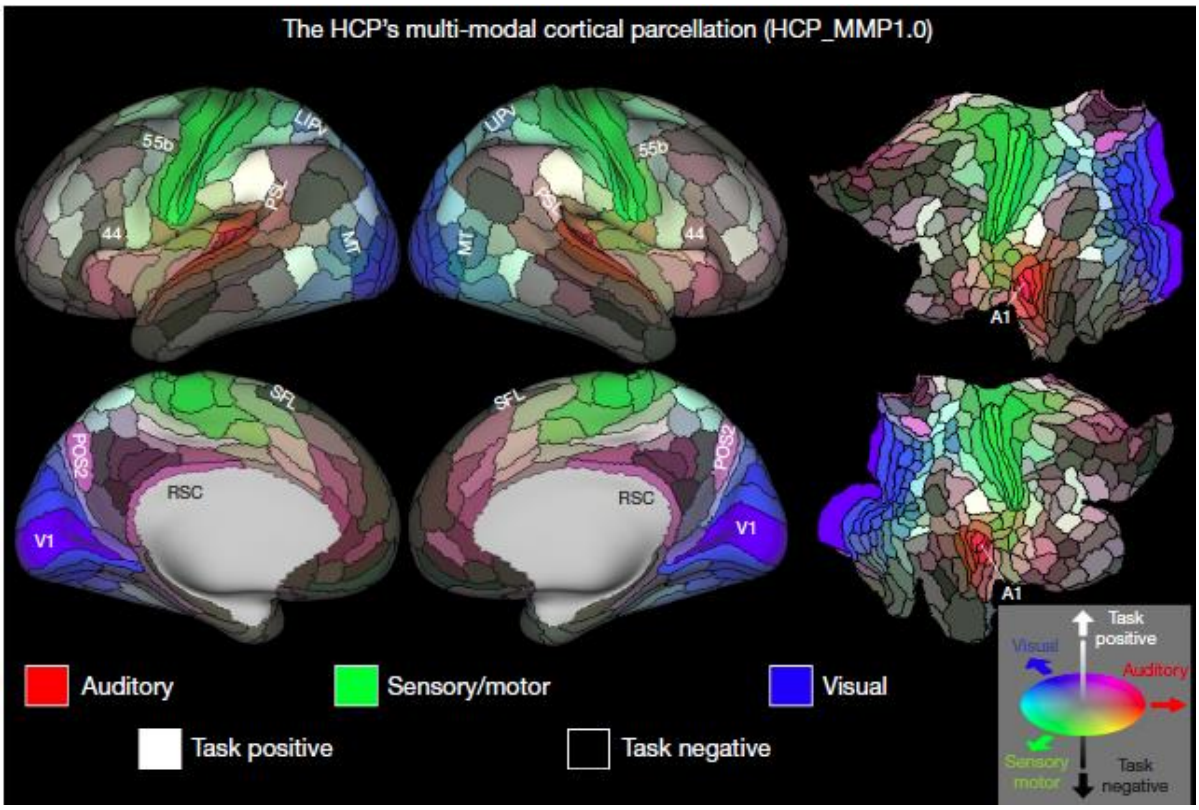

Figure 2-1: Glasser parcellation (Glasser et al., 2016). The 180 areas delineated and identified in both left and right hemispheres are displayed on inflated and flattened cortical surfaces. Black outlines indicate areal borders. Colours indicate the extent to which the areas are associated in the resting state with auditory (red), somatosensory (green), visual (blue), task positive (towards white), or task negative (towards black) groups of areas. The legend on the bottom right illustrates the 3D colour space used in the figure (figure taken from Glasser et al., 2016; page 173).

2.7 Inter-Subject Correlation

We computed ISC (Bartels & Zeki, 2004a; Hasson et al., 2004; Hejnar et al., 2007) on movie-driven fMRI data denoised with and without ICA-AROMA. ISC was computed with a custom MATLAB 2020a (Mathworks, Natick, MA, USA) script using a leave-one-out (LOO) approach (Kauppi et al., 2017). More specifically, we first computed an average time series in homologous parcellated regions across healthy controls, such that each healthy control was left out from the original sample one at a time. Pearson correlations were then computed between the time series of the left-out healthy control and the group average time series, to obtain one ISC value per region per healthy control. This step allowed me to characterize normative BOLD synchronization distributions (n=24 observations) for each parcellated region. ISC for each PWE

was calculated by correlating each individual time series with the average time series across all healthy controls, separately for each parcellated region.

The LOO approach for computing ISC results in higher *r* values than we might observe using a pairwise approach (in which ISC values are obtained by computing Pearson correlations between the time series in homologous regions across all unique pairs of subjects, and averaging all pairwise correlations to obtain one value per region; Hasson et al., 2004; Nastase et al., 2019; Ren et al., 2017). Using a pairwise method, each subject contributes to $N(N-1)/2$ correlation pairs, as opposed to each subject contributing to N estimates in the LOO approach. A pairwise approach to calculating ISC thus results in highly interdependent correlation values and artificially inflated degrees of freedom (Nastase et al., 2019). Moreover, as fMRI data follow a power law (neuronal data are acquired in a temporal order based on slice timing in the scanner), correlational analyses may invoke spurious correlations (Schaworonkow et al., 2015). Parametric tests (like t-tests) should thus be avoided for correlations derived using a pairwise, but not a LOO approach. The non-independence of correlations and spurious correlations are less of an issue, since groups or conditions are similarly influenced by a LOO approach (Nastase et al., 2019). Ultimately, by creating comparison time courses with the LOO method (based on a group average of all time courses), we can preserve the fMRI signal and reduce the noise to a great extent.

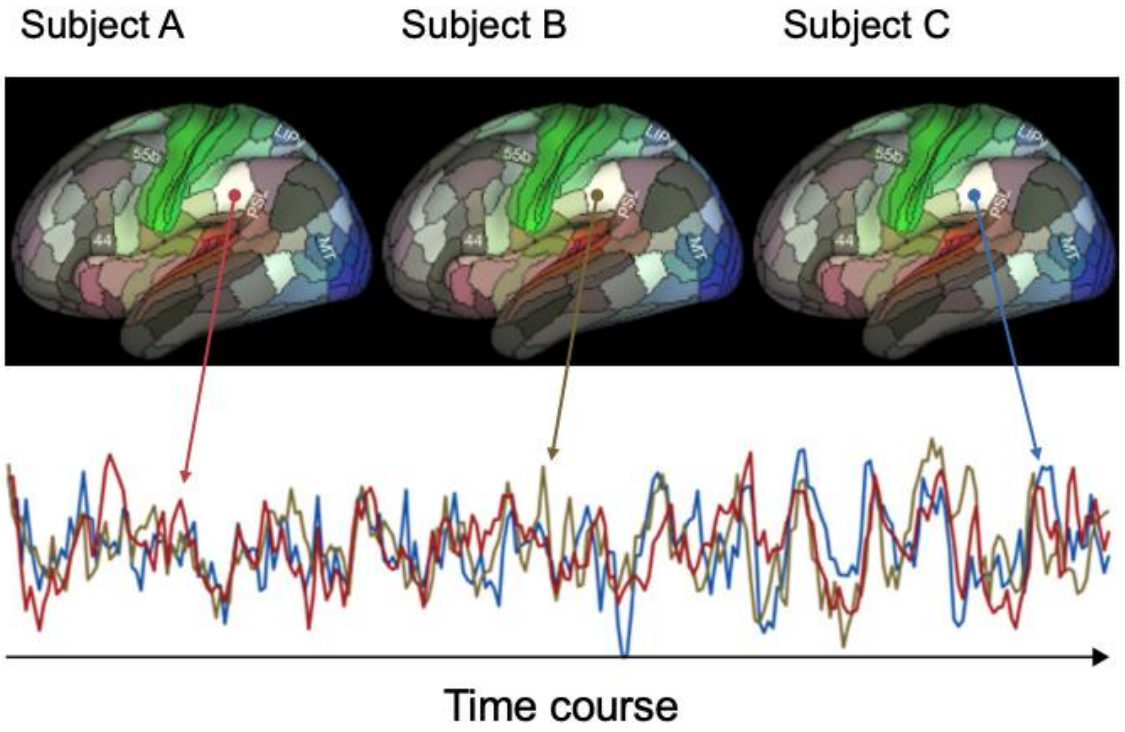

Figure 2-2: Schematic of inter-subject correlation using the Glasser parcellation (Glasser et al., 2016). Inter-subject correlation reflects synchronous blood oxygen level dependent (BOLD) activity in homologous regions across subjects, across the time course of a functional magnetic resonance imaging (fMRI) scan. In this figure, red, blue, and gold lines indicate three different individual BOLD timeseries in one specific region.

2.7.1 Effect of Denoising with and without ICA-AROMA at Whole-Brain and Regional Levels

We examined whether denoising with or without ICA-AROMA would produce higher ISC values at whole-brain and regional levels. A measure of global ISC was obtained for each participant by averaging their ISCs across all 360 parcellated regions. Global ISC during movie viewing in data denoised with and without AROMA was compared using a 2 x 2 mixed analysis of variance (ANOVA), with group (PWE vs. healthy control) as a between-subjects factor and denoising procedure (AROMA vs. no AROMA) as a within-subjects factor.

At the regional level, to explore the advantage of data processed using ICA-AROMA on ISC values over denoising without AROMA, I computed a paired samples t-test for each of the 360 parcellated regions, across all subjects. To account for multiple comparisons, a false

discovery rate (FDR) correction was applied at a threshold of $q < 0.05$ (Benjamini & Hochberg, 1995). The number of regions for which denoising with AROMA revealed higher ISC values than data denoised without AROMA was reported. To further evaluate regional differences in ISC dependent on denoising with or without AROMA, the difference between AROMA and non-AROMA ISC values was computed, and the patterns described.

2.7.2 Qualitative Evaluation of Regional ISC During Movie-Driven Stimulation

Before searching for abnormalities of regional ISC in PWE, we first qualitatively evaluated patterns of regional ISC during movie viewing in healthy controls and in PWE. To do this, we examined the distributions of regional ISC values obtained in our healthy control group and in PWE during movie viewing, relative to values we might have expected based on previous literature. We also visually inspected patterns of ISC in PWE and healthy controls plotted on the brain's cortical surface.

Furthermore, we explored patterns of regional variation in ISC by normalizing the ISC values in each of the 360 parcellated regions within each subject. *z*-scoring the ISCs within each individual allowed us to evaluate patterns of regional neural synchronization across individuals. ISC *z*-scores were computed using the mean and standard deviation of the ISC values of each individual subject across all regions. For ease of interpretation, the parcellated regions were clustered according to the 22 functional hemispheric sections delineated by the Glasser parcellation (Glasser et al., 2016). Functional sections containing regions with reliably high ISC *z*-scores across healthy controls and PWE were identified.

2.7.3 Identification of ISC Abnormalities in People with Epilepsy

Lastly, to establish the clinical utility of movie-driven fMRI in presurgical evaluations of epilepsy, we wondered if ISC could reveal abnormalities of neural synchronization in PWE. To explore this question, we first compared each PWE's left and right hemisphere regional *z*-scored ISC profile (as computed above) against the average profile of healthy controls, to obtain one correlation value per PWE, per hemisphere. The correlation values obtained provided a measure

of the *featural similarity*, or the sameness, of each individual's ISC profile with the healthy control group average. Higher correlations indicate that an individual exhibited a pattern of ISC similar to the group of healthy controls. Ultimately, such an approach allowed us to assess whether individual PWE overall experienced the movie stimulus similarly to the group of neurotypical controls. PWE whose featural similarity coefficients fell below the average featural similarity coefficients obtained in the left and right hemispheres in healthy controls (using a LOO approach) minus 1.96 standard deviations were classified as having an abnormal ISC profile during movie viewing.

Following this, we aimed to identify region-specific ISC abnormalities in PWE. To do this, we computed a threshold for the lower bound 99% confidence interval, by subtracting 2.576 standard deviations from the healthy control group average ISC at each of the 360 regions. We decided to use such a stringent threshold to give us confidence that the abnormalities observed in PWE were not simply spurious. In doing so, we identified 139 cortical regions in which the 99% confidence intervals did not span zero (regions that were meaningfully active in healthy controls, and that would allow for the identification of ISC abnormalities in patients). At each of these 139 regions, we then identified PWE who exhibited significantly low ISCs (below the lower bound 99% confidence interval). This count would give us an idea about the sensitivity of each region for identifying ISC abnormalities in patients. We anticipated that the sensitivity of any of the 139 regions for revealing ISC abnormalities would be largely driven by the strength of the correlations observed within the region. We also counted the number of abnormalities exhibited by each PWE over the 139 cortical regions. We applied an FDR correction (Benjamini & Hochberg, 1995), whereby we predicted effectively no spurious abnormalities in PWE across the identified 139 regions (.5% of 139 regions = .70 abnormalities expected due to chance in each PWE). We then calculated the probability that the number of abnormalities observed in each PWE could have resulted from chance (referring to binomial probability theory, with a probability of observing abnormality at any of the 139 regions considering the lower bound of the 99% confidence interval as .005, or .5%).

Chapter 3

3 Results

3.1 Effect of Denoising with and without ICA-AROMA at Whole-Brain and Regional Levels

We investigated the influence of Group (PWE vs. controls) and Denoising protocol (AROMA vs. no AROMA) on global ISC value by means of a 2 x 2 mixed analysis of variance (ANOVA), with group (PWE vs. healthy control) as a between-subjects factor and denoising procedure (AROMA vs. no AROMA) as a within-subjects factor. A significant main effect of Denoising was found, $F(1, 40) = 106.53$, $p < .001$, $\eta_p^2 = .73$. Data denoised with AROMA revealed higher ISC values than data denoised without AROMA ($M = 0.287$, $SD = 0.012$ vs. $M = 0.259$, $SD = 0.012$, respectively). This result suggests that denoising naturalistic fMRI data with AROMA reveals neural synchronization more clearly than denoising without AROMA, supporting its use for sensitively identifying abnormality in epilepsy. Distributions of global ISC in PWE and controls of data denoised with and without AROMA can be seen in Figure 3-1. We found no significant main effect of Group, $F(1, 40) = 1.48$, $p = .231$, $\eta_p^2 = .04$, nor a significant interaction of Group by Denoising protocol, $F(1, 40) = 2.01$, $p = .164$, $\eta_p^2 = .05$. To confirm the correlation values observed in PWE and controls after denoising with and without AROMA were meaningful (i.e., $r \neq 0$), we conducted four one sample *t*-tests using a test value of zero. Results confirmed that correlation values found in PWE and controls after denoising with and without AROMA were significantly different from zero (all $p < .001$). As the ANOVA did not reveal differences in ISC between PWE and controls at the global level, we were prompted to consider that alterations in BOLD synchronization in PWE might be more apparent at the level or parcellated regions or functional sections.

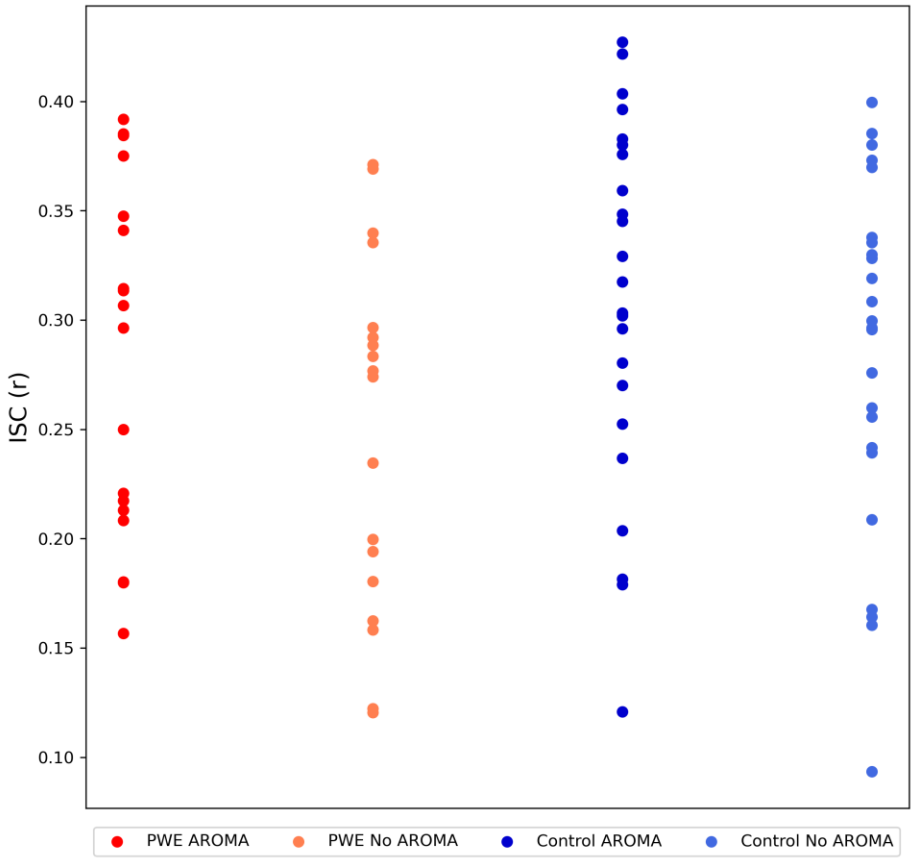

Figure 3-1: Distributions of global ISC in PWE and healthy controls during movie viewing, in data denoised with and without ICA-AROMA.

To evaluate whether the advantage of AROMA denoising on global ISC value was apparent at the regional level, we compared the magnitude of regional ISC values obtained in data denoised with and without AROMA. Paired samples t-tests were performed at each of the 360 parcellated regions, across all subjects. We observed that correlations in data denoised with AROMA were significantly higher compared to correlations in data denoised without AROMA in 56 of the 180 (31.11%) regions in the left hemisphere and 42 of the 180 (23.33%) regions in the right hemisphere. In contrast, correlations in data denoised without AROMA were significantly higher compared to data denoised with AROMA in only 18 of the 180 (10%) regions in the left hemisphere and 16 of the 180 (8.89%) regions in the right hemisphere. This result indicates a fairly widespread strengthening of ISC with the application of AROMA on data derived using naturalistic stimulation. Since denoising with AROMA yielded a greater number of regions with higher ISC values than denoising without AROMA, our analyses going forward will use data denoised with AROMA.

To further evaluate regional differences in ISC dependent on denoising, the difference between AROMA and non-AROMA ISC values was computed (non-AROMA ISC subtracted from AROMA ISC; Figure 3-2). On visual inspection, denoising with AROMA reliably yielded larger ISC values in many regions aside from several frontal and parietal regions (the bilateral anterior cingulate and medial prefrontal cortices, early somatosensory and motor cortex, inferior parietal cortex, orbital polar and frontal cortex, sensorimotor associated paracentral lobular and mid cingulate cortex, as well as the left insular and frontal opercular cortex, left medial and temporal cortex, superior parietal cortex and intraparietal sulcus, and the right dorsolateral prefrontal cortex).

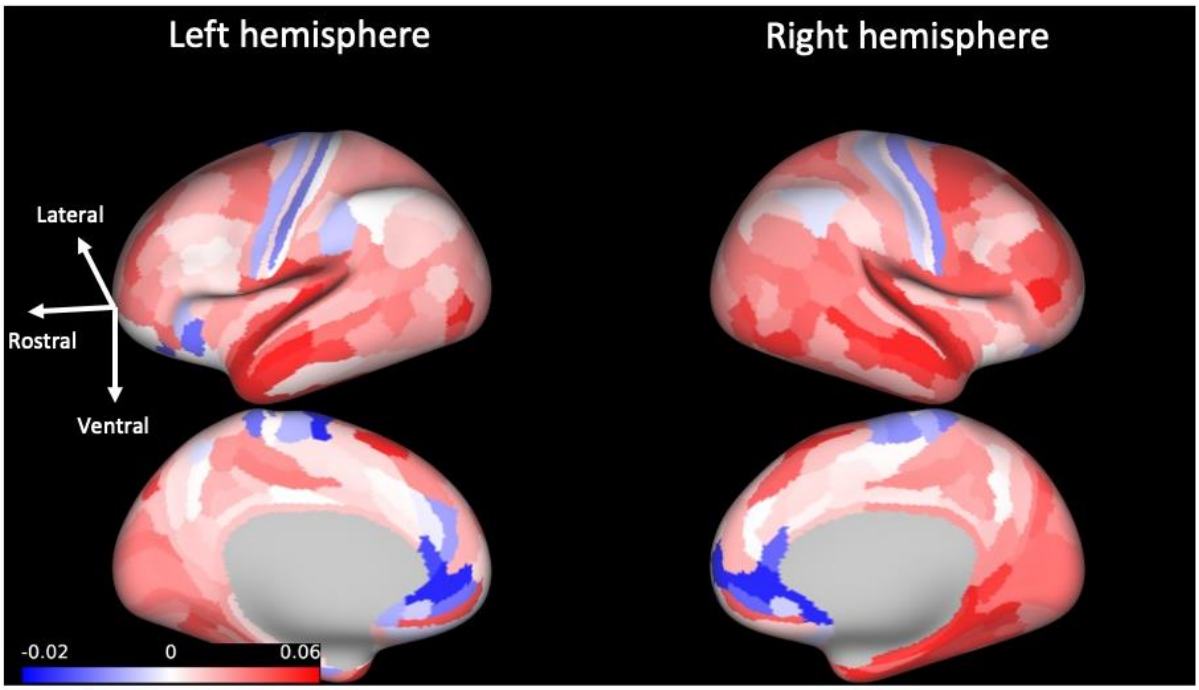

Figure 3-2: The difference in inter-subject correlation (*r*) between data denoised with versus without AROMA (non-AROMA ISC subtracted from AROMA ISC) across all subjects, plotted for each of the 360 Glasser parcellated regions (Glasser et al., 2016), shown in a lateral view. *Positive values* reflect regions that exhibited higher inter-subject correlation values after denoising with AROMA. *Negative values* reflect regions that exhibited higher inter-subject correlation values after denoising without AROMA.

3.2 Qualitative Evaluation of Regional ISC During Movie-Driven Stimulation

Our qualitative evaluation revealed that regional ISCs averaged across healthy controls ranged from .02 to .76 (M = .31; SD = .20; Figure 3-3). In healthy controls, the maximal correlations observed (r > .6) were in regions in bilateral early auditory and auditory association cortices, and in the left MT+ complex. This result reflects the shared neural synchronization of sensory regions as our healthy controls engaged with the film, and is consistent with previous studies using the same film stimulus as we did (i.e., Hasson et al., 2008b, 2010; Naci et al., 2014), which also found maximal correlations in auditory cortices. At the higher end, our observed ISC values are larger in magnitude than those observed in neurotypical individuals in similar studies that employed a pairwise approach to calculate ISC (i.e., maximal correlations of ~.4 in Golland et al., 2007, Hasson et al., 2008c, 2009, Herbec et al., 2015, Nummenmaa et al., 2012, Salmi et al., 2013), confirming that a LOO approach to computing ISC can result in enhanced correlation coefficients (Nastase et al., 2019). The regional correlations observed as PWE watched the Hitchcock film maintained a similar range to what we observed in healthy controls (from .03 to .70; M = .28; SD = .19) and were also maximal in early auditory and auditory association cortices. Overall, our observed ISC values were comparable to other similar naturalistic stimulation paradigms in our healthy controls, and also in PWE.

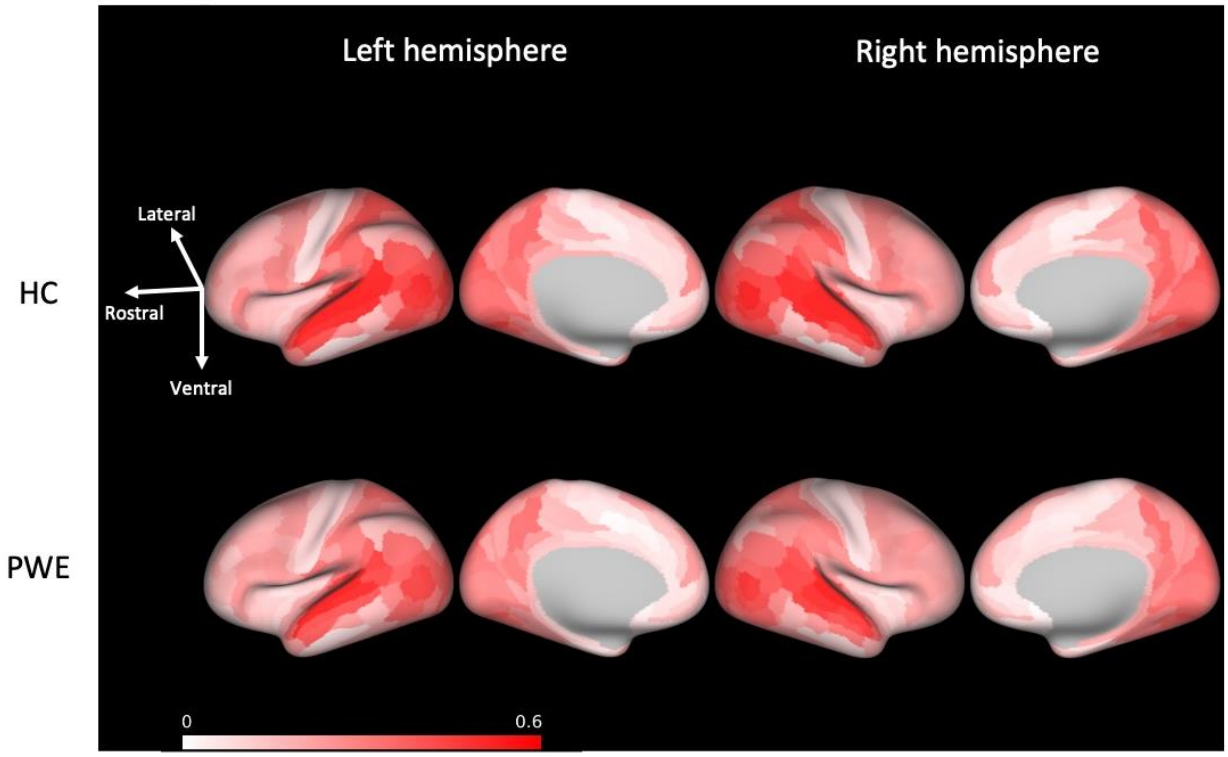

Figure 3-3: Inter-subject correlation (*r* value) in PWE and healthy controls (HCs) during movie viewing, in data denoised with AROMA represented on a colour scale ($0 < r < .6$) plotted for each of the 360 regions delineated by the Glasser parcellation (Glasser et al., 2016), shown in a lateral view.

We also explored patterns of regional variation in ISC by computing ISC *z*-scores for each of the 360 regions within each healthy control and PWE (Figures 3-4 and 3-5). Functional sections delineated by the Glasser parcellation (Glasser et al., 2016) that contained regions with reliably high ISC *z*-scores in healthy controls included those in the bilateral early auditory and auditory association cortices, early and higher-order visual areas (V1, early visual cortex, dorsal and ventral streams, MT+ complex), and sensory "bridge" regions. PWE showed similar patterns of regional variation in ISC as healthy controls, giving us confidence that all subjects experienced the movie stimulus similarly during imaging.

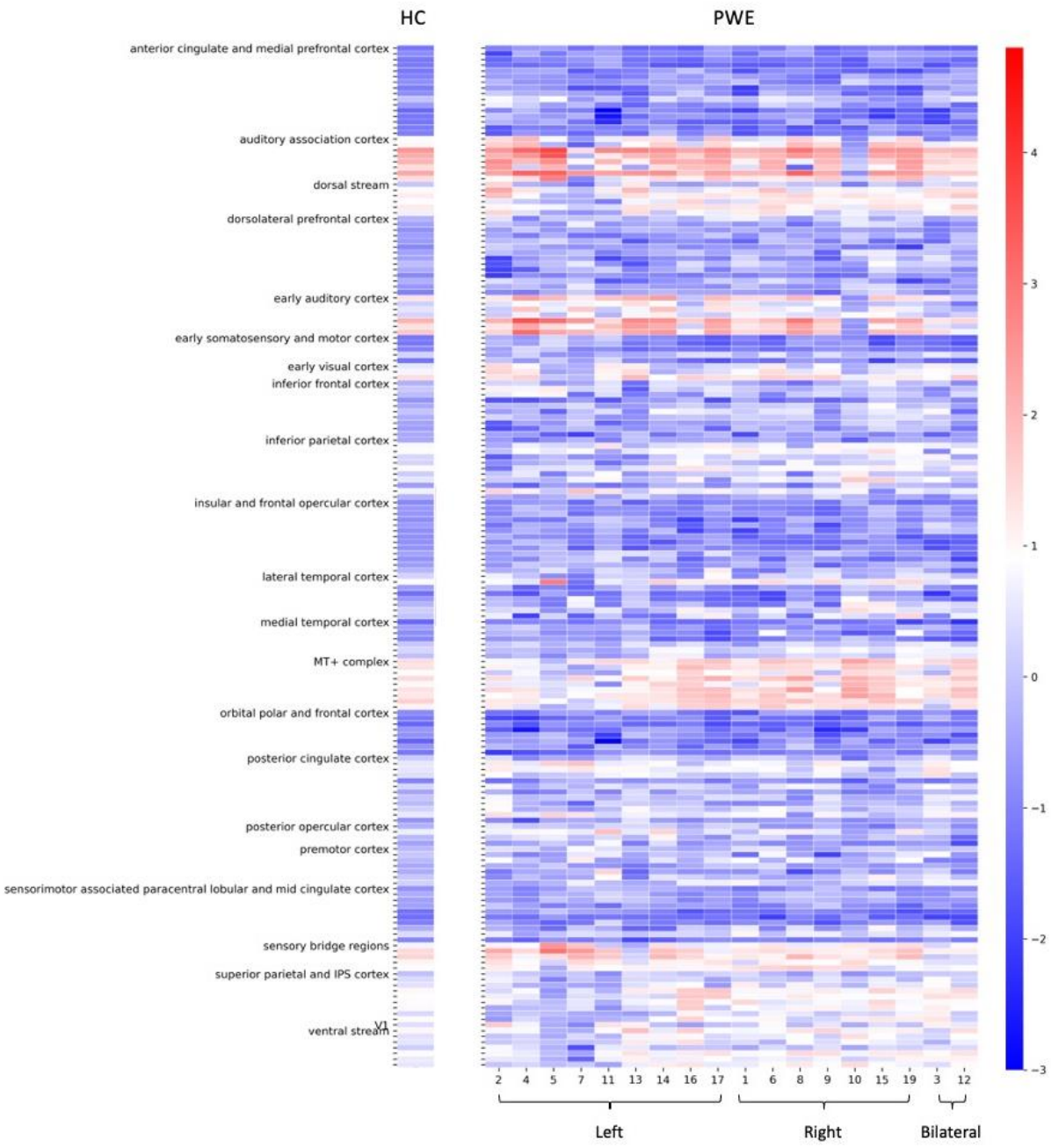

Figure 3-4: Left hemisphere regional *z*-scored ISCs in individual PWE and healthy controls (HCs) as a group. Each row represents one (out of 360) parcellated regions. The rows are grouped into functionally distinct sections, which are labelled on the left-hand side. The subject numbers of PWE are displayed grouped according to seizure lateralization (left, right, or bilateral). The *colour bar* on the right-hand side shows the colours associated with *z*-scored ISC values.

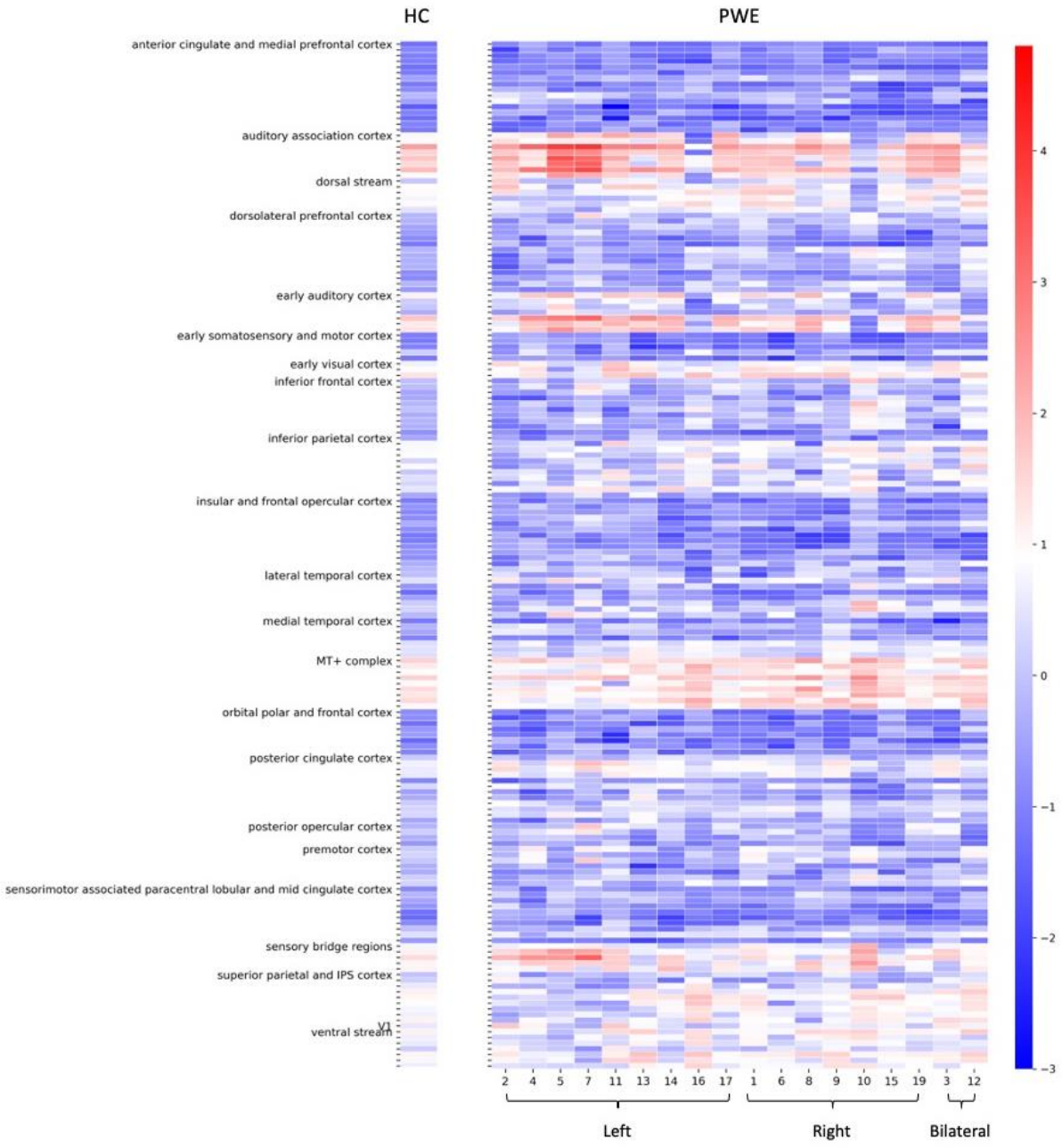

Figure 3-5: Right hemisphere regional *z*-scored ISCs in individual PWE and healthy controls (HCs) as a group. Each row represents one (out of 360) parcellated regions. The rows are grouped into functionally distinct sections, which are labelled on the left-hand side. The subject numbers of PWE are displayed grouped according to seizure lateralization (left, right, or bilateral). The *colour bar* on the right-hand side shows the colours associated with *z*-scored ISC values.

3.3 Identification of ISC Abnormalities in People with Epilepsy

We aimed to use our naturalistic stimulation paradigm to identify abnormalities in PWE, first by assessing the featural similarity, or the degree to which each patient's left and right hemisphere regional *z*-scored ISC profile correlated with the healthy control group average (Figure 3-6). Overall, five out of 18 PWE exhibited abnormal featural similarity relative to the healthy control group average, in either the left or right hemisphere, with three of these subjects displaying abnormality in both hemispheres (Table 3-1). Four out of the five PWE classified as abnormal based on the similarity of their ISC profile with the healthy control group average had seizures lateralized to the left hemisphere, while one abnormal PWE had seizures lateralized to the right hemisphere.

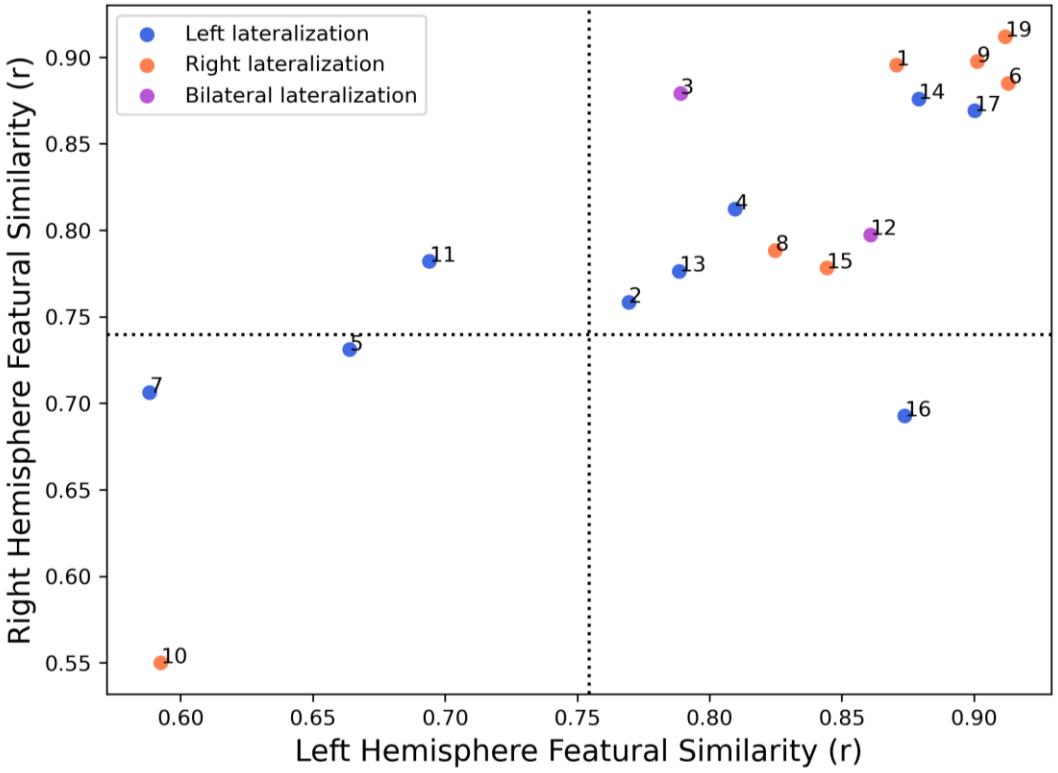

Figure 3-6: Featural similarity coefficients of PWE *z*-scored ISC profiles for the left (*x-axis*) and right (*y-axis*) hemispheres. Points for PWE are coloured according to their seizure lateralization (left, right, or bilateral) and are labelled with their subject numbers. The *dashed lines* represent the average featural similarity coefficients obtained in the left and right hemispheres in healthy controls (using a LOO approach) minus 1.96 standard deviations. PWE falling below this threshold were classified as having an abnormal ISC profile within either the left or right or bilateral hemispheres relative to the healthy control group during movie viewing.

Table 3-1: Characteristics of Patients Identified as Abnormal Based on Featural Similarity of Inter-Subject Correlation Profile

Participant #	Hemisphere identified as abnormal via featural similarity of regional ISC (AROMA)	Age	Sex	Handedness	Seizure lateralization	Duration of epilepsy	FSIQ	Notes
PWE 5	LH & RH	59	F	R	L	56	76	.
PWE 7	LH & RH	52	M	R	L	48	91	.
PWE 10	LH & RH	37	M	R	R	35	83	Reported difficulty hearing movie over scanner noise
PWE 11	LH	18	M	R	L	6	88	.
PWE 16	RH	29	M	R	L	5	120	.

Note. AROMA = Automatic Removal of Motion Artefacts, a denoising procedure used to process some of the data; PWE = sample of people with epilepsy; F = female; M = male; L = left hemisphere; R = right hemisphere; FSIQ = full scale intelligence quotient.

We also identified region-specific ISC abnormalities in PWE by counting the number of PWE who exhibited significantly low ISCs (below the lower bound 99% confidence interval) within 139 reliably active cortical regions (Figure 3-7). Regions in which PWE (at maximum, we observed abnormalities in 3 PWE at given regions) exhibited abnormal ISC included those in the bilateral early auditory and auditory association cortices, early and higher order visual cortices (V2-4, dorsal and ventral streams, MT+ complex), inferior parietal cortex, posterior cingulate cortex, and superior parietal cortex and intraparietal sulcus, as well as in the left inferior frontal cortex, lateral temporal cortex, sensory "bridge" regions, and V1, and the right insular and frontal opercular cortex. As expected, the sensitivity of regions for revealing ISC abnormalities was largely driven by the strength of the correlations observed within the region (mean ISCs observed across regions in healthy controls correlated moderately positively with the number of PWE found to exhibit ISC abnormalities at each of the 139 highly active regions, $r = .48$, $p < .0001$). Moreover, seven out of 18 PWE were found to exhibit a significant number of abnormalities (greater than what we might expect due to chance) across the 139 reliably active regions identified in healthy controls (Table 3-2).

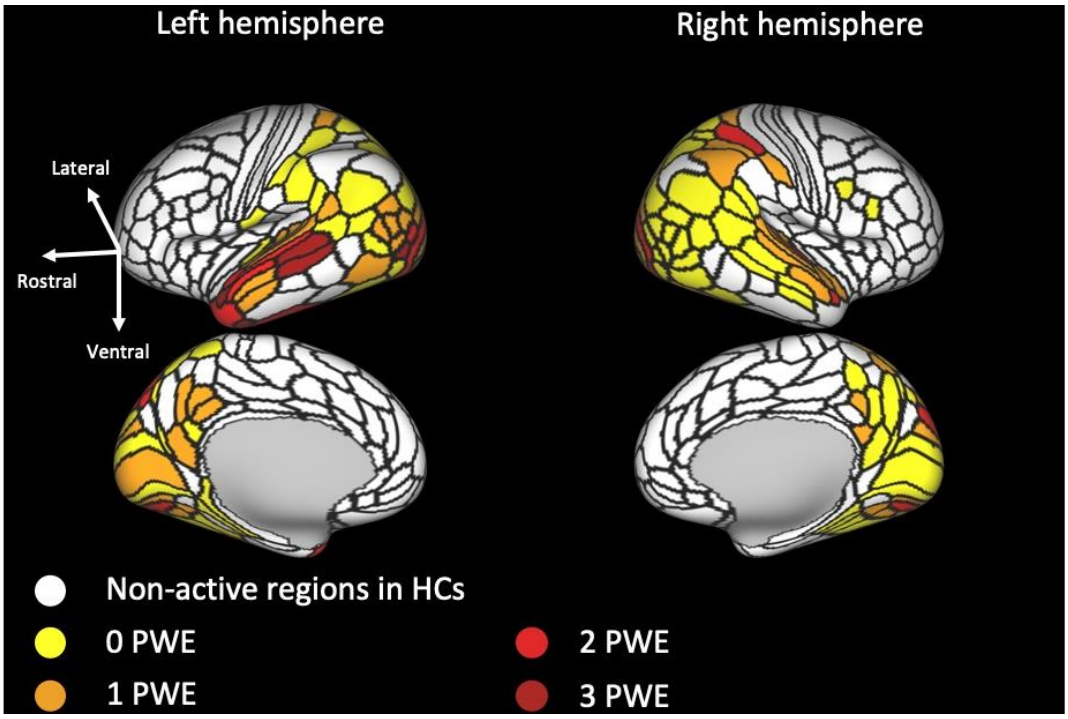

Figure 3-7: Number of PWE exhibiting low ISCs (below the lower bound 99% confidence interval in the healthy controls) plotted at the 139 reliably active regions identified in healthy controls, shown in a lateral view.

Table 3-2: Number of ISC abnormalities in PWE in reliably active regions. The probability that the number of abnormalities could have been observed due to chance has been calculated using binomial probability, and *p*-values are reported. Significant *p*-values ($p < .05$) are bolded.

PWE	# Abnormalities (out of 139 Regions)	Binomial Probability of Observing # Abnormalities by Chance
1	1	$p = .35$
2	4	$\mathbf{p < .01}$
3	0	$p = .50$
4	0	$p = .50$
5	24	$\mathbf{p < .000001}$
6	1	$p = .35$
7	27	$\mathbf{p < .000001}$
8	7	$\mathbf{p < .00001}$
9	0	$p = .50$
10	19	$\mathbf{p < .000001}$
11	3	$\mathbf{p < .05}$
12	0	$p = .50$
13	2	$p = .12$
14	0	$p = .50$
15	1	$p = .35$
16	5	$\mathbf{p < .001}$
17	0	$p = .50$
18	0	$p = .50$

3.4 Summary of Results

To maximize the sensitivity of ISC analyses of naturalistic fMRI data, we examined the effect of an automated ICA-based strategy for removing head motion-induced variation from fMRI signal (ICA-AROMA; Pruim et al., 2015b). We found widespread strengthened correlations in data denoised with compared to without AROMA, supporting the use of ICA-AROMA for denoising data derived using naturalistic stimulation. Furthermore, to establish the utility of naturalistic fMRI paradigms in the presurgical assessment of PWE, we characterized patterns of neural synchronization and found that our correlation values were similar to those found in other similar naturalistic stimulation paradigms in our healthy control sample, and also in PWE, albeit larger in magnitude. Finally, we sought to identify neural synchronization abnormalities in PWE. We expected PWE would exhibit widespread differences in neural

synchronization compared to controls during movie viewing, given the structural and functional pathology associated with prolonged epileptic activity. We were able to identify five of 18 PWE who varied significantly from the healthy control group in terms of their overall ISC profile. On examination of region-specific ISC, we found that PWE (at a maximum, 3 PWE at any given region) exhibited significant ISC abnormalities in sensory and higher order cortical regions, and also that seven of 18 PWE exhibited abnormality (greater than what we might expect due to chance) in a significant number of regions reliably activated in healthy controls.

Chapter 4

4 Discussion

4.1 Denoising with ICA-AROMA Results in Augmented Inter-Subject Correlations

To establish the utility of naturalistic fMRI in clinical evaluations of epilepsy, we evaluated movie-driven fMRI in conjunction with one particular strategy for removing motion-induced signal variation from fMRI data (ICA-AROMA; Pruim et al., 2015b). Following preprocessing, two identical sets of movie-driven fMRI data were equivalently smoothed and denoised with a general linear model that included 6 realignment parameters, cerebrospinal fluid, and white matter confounds. One of these data sets was additionally 'non-aggressively' denoised with ICA-AROMA.

At the whole-brain level, we observed data denoised with AROMA resulted in ISC values greater in magnitude compared to data denoised without AROMA. Similarly, we observed a strengthening in the value of ISC in widespread brain regions with the application of ICA-AROMA on data derived using naturalistic stimulation, over data denoised without AROMA. Thus, we found that ICA-AROMA did not noticeably alter the temporal characteristics of movie-driven fMRI data, since regional variation in ISC was generally maintained, albeit strengthened by AROMA. ISC is, by definition, driven by the stimulus (Hasson et al., 2010). Even correlated artefact captured by ISC (i.e. all subjects moving at the same time in the scanner) is presumably stimulus-driven. By applying ICA-AROMA, we improved the correlation values and in principle, enhanced stimulus-driven effects. Furthermore, augmented correlation values after denoising with AROMA allow more room (between $0 \geq r \leq 1$) to identify variability in neural synchronization between patients and controls. Overall, we suggest the use of AROMA may be appropriate for denoising data derived using naturalistic stimulation, particularly when the goal is to identify abnormalities of neural synchronization in clinical samples.

4.2 People with Epilepsy and Healthy Controls Experienced the Movie Stimulus Similarly

Our qualitative evaluation of regional ISC revealed similar correlation values (in terms of spread and the regions of highest correlation) as healthy controls and PWE watched the same Hitchcock film in the scanner. In both groups, the highest ISCs were observed in early auditory and auditory association cortices, consistent with previous studies using the same film stimulus as we did (Hasson et al., 2008b, 2010; Naci et al., 2014) and studies using other movies (Finn et al., 2017; Golland et al., 2007; Hasson et al., 2004; Herbec et al., 2015; Jääskeläinen et al., 2008; Lahnakoski et al., 2012b; Nummenmaa et al., 2012). The comparable patterns of ISC observed in both PWE and healthy controls gives us confidence that both groups similarly engaged with the film stimulus in the scanner.

We further evaluated patterns of regional variation in ISC by computing ISC *z*-scores for each of the 360 regions within each healthy control and PWE. In doing so, we observed similar patterns across all subjects, whereby the highest ISC *z*-scores were apparent in bilateral early auditory and auditory association cortices, early and higher-order visual areas (V1, early visual cortex, dorsal and ventral streams, MT+ complex), and sensory "bridge" regions. Previous investigations similarly showed highly synchronous responses to naturalistic stimulation across subjects in sensory and sensory associated cortical regions of the temporal, parietal, and occipital cortices (i.e., Anderson et al., 2013; Bartels & Zeki, 2005; Byrge et al., 2015; Finn et al., 2018; Golland et al., 2007; Hanson et al., 2009; Hasson et al., 2004, 2008a, 2008c, 2009; Hasson & Honey, 2012; Jääskeläinen et al., 2008; Kauppi et al., 2010b; Lahnakoski et al., 2014; Malinen et al., 2007; Naci et al., 2014; Nummenmaa et al., 2012; Salmi et al., 2013; Wilson et al., 2008). Such brain-region specific BOLD synchronization has been posited to have important implications for understanding the similarity of high-level information processing and shared psychological perspectives and mental states across individuals (Hasson et al., 2004; Lahnakoski et al., 2014; Nummenmaa et al., 2012, 2014) – in the present investigation, between PWE and neurotypical controls.

As delineated by the Glasser parcellation (Glasser et al., 2016), the regions making up the early auditory and auditory association cortices are those such as primary auditory cortex (A1),

the para, medial, and lateral belt complexes, regions of the superior temporal sulcus (STS), and others. We expected increased synchronization of neural responses in these areas, as we presented individuals with a complex audiovisual stimulus containing speech, music, and other sound elements. Previous studies that employed complex audiovisual (Honey et al., 2012; Lerner et al., 2011; Wilson et al., 2008) and speech stimuli (Ferstl et al., 2008; Mar, 2011; Schmälzle et al., 2013; Specht, 2014) found that their stimuli elicited a large network of auditory, linguistic, and extralinguistic cortical regions. The STS and the adjoining temporoparietal junction have also been shown to play important roles in social cognition (Allison et al., 2000; Lahnakoski et al., 2012a; Nummenmaa & Calder, 2009) and speech processing (Boldt et al., 2013; Lahnakoski et al., 2012b).

Further, we found patients and controls showed synchronous responses in early and higher-order visual areas (V1, early visual cortex, dorsal and ventral visual streams), MT+ complex, and sensory "bridge" areas. V1 and early visual cortex (V2, V3, V4) are well-studied occipital lobe regions specialized in extracting pattern, colour, and orientation information from the visual world (Daugman, 1988; Hubel & Wiesel, 1978; Lee, 1996). The dorsal and ventral visual streams are two prominent pathways thought to be involved in vision-for-action and vision-for-perception, respectively (Goodale & Milner, 1992). MT+ complex is made up of higher-order visual areas such as the medial superior temporal (MST) and middle temporal (MT) areas, lateral occipital areas, and others (Glasser et al., 2016). Neuroimaging studies have implicated regions of the lateral occipital complex (LOC) in high-level shape and object recognition (Kanwisher et al., 1996; Malach et al., 1995) and regions of the medial temporal cortex (MT/MST) in the processing of visual motion (Movshon & Newsome, 1996; Newsome & Pare, 1988; Rees et al., 2000; Tootell et al., 1995; Zeki, 1991) and shape processing (MT/MST). Recently, MT+ has also been shown to extract depth information from visual scenes using not only binocular but also monocular depth cues (Tsushima et al., 2014). The parcellated regions making up the sensory "bridge" regions include the perisylvian language areas, the superior temporal visual area, and areas of the temporo-parieto-occipital junction (Glasser et al., 2016). The perisylvian language areas are involved in semantically- (i.e., auditory comprehension and vocalization of semantic content) and phonologically-based (i.e., automatic repetition) language functions (Catani et al., 2005). The temporo-parieto-occipital junction is a complex cortical

territory involved in high-level functions, such as language (Fehr et al., 2007), visuo-spatial recognition (Thiebaut De Schotten et al., 2005), writing (Scarone et al., 2009), reading (Mandonnet et al., 2007), symbol processing (Holloway et al., 2010), calculation (Fehr et al., 2007; Rosenberg-Lee et al., 2011), self-processing (Blanke & Arzy, 2005), working memory (Deprez et al., 2013), and face and object recognition (Zhen et al., 2013). It is intuitive that these such regions appeared to be consistently activated across individuals, given the nature of our film stimulus, which contained numerous stationary and moving objects (i.e., gun, people, faces), various cinematic manipulations (i.e., zooming in/out, changing angles, panning), speech, music, and other sounds.

4.3 Our Approach to Calculate Inter-Subject Correlation Resulted in Maximal Correlations and was Sensitive to Individual Differences in Epilepsy

Our approach to calculating ISC in PWE and healthy controls produced regional correlation values larger in magnitude than those observed in similar studies which employed a pairwise approach to calculate ISC (i.e., maximal correlations of .76 in our healthy controls compared to ~.4 in Golland et al., 2007, Hasson et al., 2008c, 2009, Herbec et al., 2015, Nummenmaa et al., 2012, Salmi et al., 2013). In our study, at each region, we computed an average time series in healthy controls, leaving one healthy control out from the original sample at each iteration. We then computed Pearson correlations between the time series of the left-out healthy control and the group (minus themselves) average time series, to obtain one ISC value per person, per region. Pearson correlations were similarly computed between the time series of each PWE and the entire healthy control group average time series to obtain ISC values at each region. Averaging the time course responses prior to calculating the correlation may have enhanced the resulting correlation coefficients in our study.

A similar approach to calculate ISC was used by Hasson and colleagues (2010). Hasson and colleagues (2010) first averaged the response time courses separately for their two groups of subjects, and then computed a correlation coefficient between the two resultant averaged time courses at each brain region. This method resulted in even higher maximal correlations than we observed (i.e., a correlation of .93 in primary auditory cortex elicited as two groups of healthy

individuals watched the same Hitchcock episode we presented). The reason Hasson and colleagues (2010) found much larger maximal correlations that we did can be attributed to our disinclination to compute an average time series for our group of PWE. Our patient sample showed heterogeneity in terms of age, sex, seizure pathology and laterality, age of onset and duration of epilepsy, handedness, and cognitive ability. Epilepsy researchers often invoke Leo Tolstoy's *Anna Karenina* principle ("all happy families are alike; each unhappy family is unhappy in its own way") in that each epilepsy patient is a unique case. Variation in behaviour, neurophysiologic and neuropathologic factors, and medication, inherent in epilepsy samples (see Paradiso et al., 1995) prevents reliable and generalizable groupings of individual PWE. Our approach to calculating ISC thus allowed for comparisons with healthy controls, without requiring averaging over individual PWE.

4.4 Utility of Inter-Subject Correlation for Identifying Abnormalities in People with Epilepsy

In order to establish the clinical utility of movie-driven fMRI, and ISC analysis, it was imperative that we confirm the ability of such methods to identify neural abnormalities in PWE. By analyzing the featural similarity, or the degree to which each patient's left and right hemisphere regional *z*-scored ISC profile correlated with healthy control group average, we were able to identify five out of 18 PWE as abnormal (with three of these subjects displaying abnormality in bilateral hemispheres). These five PWE may have responded idiosyncratically to the film stimulus for a variety of reasons. It is possible that our 'abnormal' patients were simply less engaged with the film stimulus than the healthy control group (i.e., they were daydreaming). It is also possible that these subjects were highly, though idiosyncratically, engaged with the film stimulus, perhaps reflecting differences in processing of the same movie scene (Hasson et al., 2008b; Lahnakoski et al., 2014) or large-scale neural reorganization due to TLE in our patients (Alessio et al., 2013; Gleissner et al., 2002; Powell et al., 2007; Richardson et al., 2003; Seidenberg et al., 1997). Besides this, one out of five PWE reported difficulty in hearing the film stimulus over the noise of the scanner, and four out of the five PWE who were identified as abnormal based on featural similarity had below average IQs. All such factors may have influenced engagement with or comprehension of the movie stimulus in these outlier

participants. As asynchronous responding is thought to relate to poor comprehension of (Hasson et al., 2009) and memory for (Hasson et al., 2008a) the stimulus, it would interesting to examine associations between outlier participant ISCs and scores on our test of memory for the movie stimulus and the other neuropsychological tests of learning and memory collected as part of the Eplink protocol.

Four out of the five PWE classified as abnormal based on the similarity of their ISC profile with the healthy control group average had seizures lateralized to the left hemisphere. Voxel-based morphometry (Bonilha et al., 2007; Keller et al., 2002; Riederer et al., 2008) and DTI (Ahmadi et al., 2009; Besson et al., 2014; Focke et al., 2008) studies have demonstrated more widespread and extensive grey and white matter abnormalities, respectively, in people with left versus right lateralized TLE, regardless of the presence of hippocampal sclerosis. The progression of grey and white matter atrophy tends to be more intense and is associated with poorer seizure control and a longer disorder duration in people with left versus right mTLE (Coan et al., 2009). Further, studies of functional organization support more restricted ipsilateral functional connectivity alterations in individuals with right mTLE, but more diffuse patterns of bilateral alterations in individuals with left mTLE, suggesting that left lateralized TLE has a stronger impact on function in wide-spanning networks (Bettus et al., 2009; de Campos et al., 2016; Haneef et al., 2015; Haneef et al., 2012; Pereira et al., 2010). These studies hint at the possibility that left and right TLE are etiologically and pathologically distinct syndromes. Further work with larger samples of PWE with the EZ lateralized to left, right, and bilateral hemispheres is necessary to evaluate this trend.

We identified a number of regions (139 out of 360 parcellated regions) which were reliably active in healthy controls (where the 99% confidence interval did not span zero). We searched for region- and patient-specific ISC abnormalities in these regions. We found that only a small number of PWE (at maximum, 3 PWE) exhibited ISC abnormalities at any given region. Regions in which PWE exhibited abnormal ISC included those we might have expected to be highly activated by the movie stimulus, including regions in bilateral early auditory and auditory association cortices, early and higher order visual cortices (V2-4, dorsal and ventral streams, MT+ complex), inferior parietal cortex, posterior cingulate cortex, and superior parietal cortex

and intraparietal sulcus, as well as in the left inferior frontal cortex, lateral temporal cortex, sensory "bridge" regions, and V1, and the right insular and frontal opercular cortex. We found that the sensitivity of regions for revealing ISC abnormalities was largely driven by the strength of the correlations observed within the region, further supporting techniques to maximize inter-subject correlation values (i.e., denoising with ICA-AROMA) where the goal is to identify abnormalities in a clinical sample.

Using a very conservative threshold (the lower bound of the 99% confidence interval of the distribution of ISCs in healthy controls), we found that seven out of 18 PWE exhibited a significant number of abnormalities (greater than what we might expect due to chance) across the 139 reliably active regions identified in healthy controls. This result supports the utility of ISC analysis applied to data derived using naturalistic stimulation for identifying even subtle abnormalities in PWE. In the present investigation, we created a normal distribution of ISC values for every region in the Glasser parcellation (Glasser et al.,2016). This is a big first step toward identifying regions that can be used to distinguish between healthy and pathological neural responses to naturalistic stimulation, to differentiate patients from healthy controls. Further investigations should aim to optimize the use of ISC as a clinical tool for evaluating neural abnormalities in presurgical evaluations of epilepsy.

4.5 Limitations

The limitations of the present examination should be noted. First, we acknowledge that functional imaging measures will only ever allow us to make inferences about neural anatomical properties. Even so, we believe that the use of naturalistic stimulation paradigms can provide important neurobiological insights and complement other more invasive tools in presurgical evaluations of epilepsy. Studying brain activity in more naturalistic settings may enhance our understandings of how the brain functions in real life. For instance, analytic methods like ISC can evaluate patterns of neural responses over time scales not conceivable with other methods. While conventional (resting-state and task-based) fMRI protocols suffer from a lack of ecological validity or experimental control, respectively, naturalistic stimulation paradigms suffer from a different conceptual drawback. Namely, the difficulty in using naturalistic

stimulation, and performing ISC analyses, relates to the complexity in untangling associations between stimulus properties and corresponding neural activity. Steps toward overcoming this limitation include methods of manipulating or modeling the stimuli (Bartels & Zeki, 2004a; Hasson et al., 2008c), reverse correlation (Hasson et al., 2004), and combinations of ISC with behavioral measures (Hasson et al., 2008a). Methods for avoiding the technical limitations of computing accurate ISC also continue to improve (Hasson et al., 2010; Kauppi et al., 2010a; Pajula et al., 2012; Sabuncu et al., 2010).

Second, our ability to partition the brain into meaningful sections across individuals is poor. The parcellation scheme used in this study (by Glasser et al., 2016) was created using functional, but not anatomical connectivity data from diffusion weighted imaging. Areal borders formed without anatomical connectivity data are determined probabilistically and are influenced by individual variability in terms of function. Indeed, Braga and Buckner (2017) investigated network organization in four individuals each scanned 24 times with fMRI and found that functional networks manifested very differently in individuals compared to as a group. Greater functional variability can be expected across individuals in higher-order frontal and parietal regions than in primary sensory regions, making parcellation schemes particularly ineffective for examinations of higher-order functions. A functional parcellation scheme may also be ineffective if applied to the data of clinical samples, like PWE, in whom neural reorganization and alteration of functional connectivity is expected. Furthermore, views that single brain regions perform isolated functions have been shifted. An understanding of human cognition ultimately relies upon knowledge of large-scale neural organization, where many/all areas compute basic functions which when combined form cognition (i.e., Bressler & Menon, 2010). There cannot be a one-size-fits-all parcellation, as function in any one region is dependent on function in a number of other regions at any given time. Moreover, parcellation schemes reflect only a snapshot of function based on the features of the task presented to subjects. We would need to run endless tasks to get a complete snapshot for each individual to obtain a ‘good’ parcellation. Despite these considerations, we thought a first investigation of the applicability of movie-driven fMRI for clinical use with PWE might benefit from a reduction in the complexity of the data by using a parcellation scheme. Also, since our regions of interest were mainly primary sensory and sensory associated cortices, we decided a functional parcellation scheme would be appropriate.

We are confident in our use of the Glasser parcellation, given we observed similar ISC patterns in our patient and control groups, in the regions we expected based on previous literature on naturalistic stimulation. Follow-up investigations will probe neural synchronization in response to naturalistic stimulation without parcellating the data. In doing so, we can determine the optimal level of smoothing to bring about maximal ISC values in higher-order frontal versus sensory cortices.

Lastly, we note that our patient sample showed heterogeneity in terms of age, sex, seizure pathology and laterality, age of onset and duration of epilepsy, handedness, and cognitive ability. We hope to confirm our findings with larger samples of PWE with seizures lateralized to left, right, and bilateral hemispheres. Fortunately, presurgical patients are being recruited from the Adult Epilepsy Service at London Health Sciences Centre, London, ON, on an ongoing basis.

4.6 Future Directions

Our ultimate goal is to establish the utility of naturalistic fMRI in the presurgical evaluation of PWE. The present investigation was a preliminary step toward this goal. We evaluated patterns of neural synchronization in PWE and neurotypical controls using ISC. To optimize methods of preprocessing naturalistic fMRI data, we also explored the ability of ICA-AROMA to remove head motion-induced variation while preserving the signal of movie-driven fMRI data. Despite the long duration of disorder and notable pathology in our patient sample, we observed similar patterns of neural synchronization as PWE and healthy controls engaged with the same film in the scanner. We were also able to identify PWE who responded idiosyncratically to the film stimulus, and we identified abnormalities in neural synchronization at individual region and patient levels.

Future investigations might better identify abnormalities of neural synchronization in PWE by using a neural network approach, like the application of an autoencoder, for anomaly detection. Such approaches have already been applied, for instance, to detect epileptic seizures from interictal EEG signal (i.e., Emami et al., 2019). Representational similarity analysis (Kriegeskorte et al., 2008) is another method suitable method for exploring fine-grained

representations of the movie stimulus in different brain regions across subjects. Further, the current study captured only a snapshot of neural synchronization between PWE and healthy controls. Future investigations might focus on examining neural synchronization along the temporal scale of the film stimulus (as in Jaaskelainen et al., 2008) or at particularly meaningful scenes (i.e., scenes with faces, objects, etc.; as in Hasson et al., 2004). There is also potential to use ISC to evaluate differences in neural synchronization within subjects, following surgery for epilepsy, as we evaluate our patient with a similar protocol one year after surgical resection. Finally, a crucial next step in evaluating the clinical utility of naturalistic fMRI will be to compare how ISC in PWE and neurotypical controls relates to performance on neuropsychological tests of learning and memory. Overall, naturalistic fMRI and associated preprocessing methods and data analytic techniques (like ISC) require further validation and follow-up investigations to be established in the clinical management of individual PWE.

4.7 Conclusion

Here, we explored the potential for naturalistic functional neuroimaging to act as a sensitive, non-invasive, and cost-effective tool for identifying functionally disturbed networks in PWE. We used ISC to assess neural synchronization at whole-brain and regional levels as people with drug-resistant TLE and healthy controls engaged with the same movie stimulus in the scanner. Our results revealed movie viewing elicited expected neural response patterns (high ISC in early auditory and auditory association cortices) in both PWE and healthy control groups. Nevertheless, were also able to identify PWE who responded idiosyncratically to the film stimulus, and we identified particular regions including those in the bilateral early auditory and auditory association cortices, early and higher order visual cortices (V2-4, dorsal and ventral streams, MT+ complex), inferior parietal cortex, posterior cingulate cortex, and superior parietal cortex and intraparietal sulcus, as well as in the left inferior frontal cortex, lateral temporal cortex, sensory “bridge” regions, and V1, and the right insular and frontal opercular cortex that appeared to be particularly sensitive to abnormalities, and we also observed significant abnormalities in seven of 18 patients. We also investigated the effects of an automated Independent Components Analysis-based denoising strategy (ICA-AROMA; Pruim et al., 2015b) on measures of neural synchronization, in hopes of optimizing the preprocessing of data

derived with naturalistic stimulation. We found that denoising with ICA-AROMA resulted in augmented ISC values in widespread cortical regions, supporting its use for removing head-motion induced variation from movie-driven fMRI data. Overall, we anticipate that naturalistic fMRI paradigms will continue to be explored for their possible utility as sensitive and reliable complements to the surgical planning tools currently used in the presurgical evaluation of epilepsy, potentially leading to better treatment and improved outcomes.

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Appendices

Appendix A: Glasser Parcellation (Glasser et al., 2016) Sections with Corresponding Regions

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
	V3B	Area V3B
	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
	6mp	Area 6m Posterior
	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 **Auditory Association 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 TG
	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 3
16 **Superior parietal and IPS cortex**	7Pm	Medial Area 7P
	7AL	Lateral Area 7A
	7Am	Medial Area 7A
	7PL	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 **Posterior Cingulate Cortex**	RSC	RetroSplenial Complex
	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 33 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 **Dorsolateral prefrontal cortex**	SFL	Superior Frontal Language Area
	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 B: Ethical Approval from the Health Sciences Research Ethics Board of the University of Western Ontario

Western

Office of Research Ethics

The University of Western Ontario
Room 4180 Support Services Building, London, ON, Canada N6A 5C1
Telephone
Website: www.uwo.ca/research/ethics

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

Ethics Officer to Contact for Further Information			
☑ Janice Sutherland	☐ Elizabeth Wamboit	☐ Grace Kelly	☐ Denise Grafton

This is an official document. Please retain the original in your files.

cc: ORE File
LHRI

UWO HSREB Ethics Approval - Initial
V 2008-07-01 (rpt4approvalNoticeHSREB_Initial) 16189 Page 1 of 1

Appendix C: Anatomical and Functional Imaging and Data Preprocessing with fMRIprep

The following is boilerplate documentation generated by fMRIPrep is intended to allow for clear, consistent description of the preprocessing steps used, in order to improve the reproducibility of studies (The fMRIPrep developers, Revision a45ea486):

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 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 5 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. 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. 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 D: Anatomical and Functional Imaging and Data Preprocessing with Freesurfer

The following is boilerplate documentation generated by Freesurfer (FreeSurfer, 2021):

Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 2001; Fischl et al., 2002; Fischl et al., 2004a; Fischl et al., 1999a; Fischl et al., 1999b; Fischl et al., 2004b; Han et al., 2006; Jovicich et al., 2006; Segonne et al., 2004, Reuter et al. 2010, Reuter et al. 2012). Briefly, this processing includes motion correction and averaging (Reuter et al. 2010) of multiple volumetric T1 weighted images (when more than one is available), removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl et al., 2002; Fischl et al., 2004a) intensity normalization (Sled et al., 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation (Fischl et al., 1999a), registration to a spherical atlas which is based on individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999b), parcellation of the cerebral cortex into units with respect to gyral and sulcal structure (Desikan et al., 2006; Fischl et al., 2004b), and creation of a variety of surface based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are

therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003; Salat et al., 2004). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006; Reuter et al., 2012).

Curriculum Vitae

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Publications

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