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Motor Network Organization in Frontal Lobe Epilepsy

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Motor Network Organization in Frontal Lobe Epilepsy

by

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Abstract

Frontal lobe epilepsy (FLE) is a seizure disorder that commonly coincides with functional motor deficits. While the source of these deficits is unknown, it is postulated that repeated seizure activity within the frontal lobe might impact the proximate motor network. To examine this hypothesis, motor networks were compared between participants with right FLE, left FLE, and controls using two methods. The first was a task-based fMRI study of brain activation during simple and complex motor tasks, and the second was a resting-state fMRI study of motor network connectivity. Both studies revealed motor network disturbances in participants with FLE, disturbances that were more pronounced in participants with higher seizure burden factors. These results show that motor networks are altered in FLE. In the future, motor fMRI studies may help identify the locations of seizure foci, predict post-surgical motor deficits, and ultimately improve the quality of life of patients with FLE.

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
FLE	Frontal lobe epilepsy
TLE	Temporal lobe epilepsy
fMRI	Functional magnetic resonance imaging
EEG	Electroencephalogram
GABA	Gamma-aminobutyric acid
AMPA	2-amino-3-(3-hyrdroxy-5-methyl-isoxazol-4-yl)propanoic acid
NMDA	N-methyl-D-aspartic acid
MRI	Magnetic resonance imaging
VEM	Video-EEG monitoring
NMR	Nuclear magnetic resonance
CSF	Cerebral spinal fluid
AED	Anti-epileptic drug
GTC	Generalized tonic clonic
CP	Complex partial (focal with dyscognitive features)
SP	Simple partial (focal without dyscognitive features)
SPECT	Single-photon emission computed tomography
PET	Positron emission tomography
[^{18}F]FDG	Fluorine-18 fluorodeoxyglucose
BA	Brodmann area
HDR	Hemodynamic response
BOLD	Blood oxygen level dependent
LTP	Long-term potentiation
LTD	Long-term depression
APB	Abductor pollicis brevis
T	Tesla
GE	General electric
GRE	Gradient-recalled echo
EPI	Echo planar imaging
TE	Echo time
TR	Repetition time
MANOVA	Multivariate analysis of variance
FSL	fMRIB software library
fMRIB	Functional MRI of brain
BET	Brain extraction tool
MCFLIRT	Motion correction: FMRIB's linear image registration tool
FWHM	Full width at half maximum
FEAT	fMRI expert analysis tool
MNI	Montreal neurological institute
FLAME	fMRIB local analysis of mixed effects

LI	Laterality index
FLIRT	FMRIB's linear image registration tool
ROI	Region of interest
GLM	General linear model
KW	Kruskal-Wallis
MW	Mann-Whitney-U

Chapter One: **Introduction**

1.1 The Clinical Problem

Epilepsy is one of the most common and serious neurological diseases, affecting approximately 0.6% of all Canadians.[1] It affects all ages, has varied causes, and includes many distinct seizure types; seizures are the primary clinical symptom of epilepsy. Epilepsy can be very disabling and cause a poor quality of life for many patients because of their inability to work, drive, or perform other daily functions. Despite this detrimental influence on large numbers of patients, much about epilepsy remains poorly understood.

Functional deficits experienced by patients readily coincide with the diagnosed epileptic disorder. For example, language impairments are often exhibited by patients with temporal lobe epilepsy (TLE),[2] and patients with frontal lobe epilepsy (FLE) commonly experience motor deficits.[3] It has been hypothesized that language impairments in TLE are due to the close proximity of the seizure focus to cortical language areas, and that repeated seizure activity may impact language function and organization throughout the brain.[4] Indeed, it has been demonstrated that cortical language regions activated during tasks differ in patients with TLE compared to controls,[5] and communication within language networks is disrupted.[6]

Motor deficits negatively influence patients with FLE on a daily basis. Neuropsychological testing has revealed impairments in cognitive functioning, motor control, coordination, and dexterity in these patients when compared to healthy controls.[3] When compared to TLE, patients with FLE perform significantly worse when evaluated on tasks measuring psychomotor speed, attention, coordination, and sequencing.[7] These studies suggest that FLE may be associated with changes in the organization and communication between motor

regions, similar to changes in cortical language functioning seen in TLE. In fact, case studies have revealed changes in motor representations in patients with FLE using cortical stimulation.[8] However, studies involving a large number of patients and using less invasive techniques had not previously been conducted. Therefore, the current study focused on cortical motor organization in participants with FLE by observing motor task activation using functional magnetic resonance imaging (fMRI). In addition, fMRI was used to examine motor network communication during rest in both participants with FLE and controls.

FMRI offers the advantage of examining motor cortex organization and network communication noninvasively. In the future, information gained from fMRI may help lead to more informed pre-surgical decisions, as well as assist in seizure onset localization, help predict post-surgical outcomes, and find the source of pre-surgical functional deficits in order to identify targets for treatment and recovery.

1.2 Prevalence of Epilepsy

In Canada, approximately 0.6% of the population (210 000 Canadians) has epilepsy.[9] Each day, there are 42 newly diagnosed cases, resulting in about 15 500 new cases per year.[9] This number ranges depending on age group, with about 60% of new cases being diagnosed in either children under 18 or adults over 60.[9] Approximately 50 million people are affected worldwide,[10] although the reported incidence of epilepsy varies greatly. Indeed, incidence ranges from 40-70 newly diagnosed cases per 100 000 people per year in industrialized countries to 100-190 per 100 000 people per year in developing countries.[10] The significant variation in incidence rates is due to the increased presence of risk factors for developing epilepsy in developing countries. Risk factors include parasitic, viral, and bacterial infections, as well as traumatic brain injury, stroke,

and brain tumours.[10] These factors are generally reduced in developed countries because of increased prevention and better treatment options.

Epilepsy is a very common neurological disorder, which highlights the importance of gaining further knowledge about epilepsy. Many individuals have a decreased quality of life due to the disorder, as it negatively affects their ability to perform many daily functions. Epilepsy's impact is not solely felt at the individual level, but also at the societal level due to its great prevalence in countries worldwide.

1.3 Pathophysiology of Seizures and Epilepsy

Epilepsy is diagnosed when an individual has two or more *unprovoked* seizures. Seizures can be provoked, in that they occur in an otherwise healthy, normal brain. Provoking factors include alcohol or drug abuse, metabolic abnormalities, infection, or fever. Alternatively, unprovoked seizures occur spontaneously, and if they occur more than once the individual is diagnosed with epilepsy upon seeking medical treatment.

Epilepsy is most readily diagnosed based on the presence of brief (<250ms) epileptogenic activity that can be observed using electroencephalography (EEG) during the period in between seizures, called the interictal period.[11] These interictal spikes occur due to a sharp potential fluctuation recorded by the EEG electrode, and they demonstrate a high propensity for occurring at or near the seizure generation site.[11] The intracellular correlate of an interictal spike is called the paroxysmal depolarizing shift; a sudden depolarization of membrane potential, lasting 50-100ms, which subsequently triggers a series of action potentials.[12] This observation, seen whilst recording a single cell, coincides with the activity recorded from a large group of cells and is

reflected by the extracellular field potential.[12] Indeed, thousands of synchronous neurons are required for one interictal spike to generate the sharp potential change seen using EEG.[12]

An epileptic seizure occurs when the brain spontaneously enters an abnormal hyperactive, hypersynchronous state,[13] or transitions from the interictal to ictal (during seizure) period.[12] Two brain regions prone to initiating epileptic seizures are the neocortex and hippocampus. This susceptibility may be due to various factors including a vast number of excitatory connections, a dependence on inhibition for regulating excitation, the capacity for strengthening synapses with recurrent activation, and the presence of spontaneous burst-generating neurons.[13] If disruption occurs in any one of these factors, prime conditions are provided for neurons to enter a hypersynchronous, hyperexcitable state.

The neocortex houses excitatory pyramidal cells that project within and between cortical layers to both other pyramidal cells and GABAergic interneurons. Typically, pyramidal neurons have very few connections with each other in order to limit their overall impact; however, each GABAergic neuron receives thousands of excitatory inputs, making for extensively interconnected cortical networks.[13] GABAergic neurons are diverse in their structure and mechanism of function, and are able to develop gap junctions with each other to allow for rapid synchronization with surrounding neurons.[13] The hippocampus is similar in that it contains a highly interconnected network of excitatory neurons and is modulated by inhibitory interneurons. These networks not only occur within the hippocampus, but also branch out into relevant neocortical structures.[12] The massive interconnectivity of these regions allows them to perform a plethora of diverse functions, but also permits the generation of abnormal, extensive excitation.

The neocortex and hippocampus both contain distinct types of neurons that are able to intrinsically generate bursts of action potentials. Layer V pyramidal cells in the neocortex and

CA3 pyramidal cells in the hippocampus are both capable of this type of activity.[12] A slow depolarizing current initially occurs due to activation of AMPA receptors, which generates an inward current of Na^+ and Ca^{2+}. This current is later sustained by NMDA receptor activation, thereby creating a local burst of action potentials.[12] Under normal conditions, bursting activity is followed by a prolonged hyperpolarization period, which occurs due to activation of voltage-gated K+ channels and GABA receptors, and therefore outward K^+ and Cl^- currents.[14] When excitation is left unchecked in these cell types, bursting activity potentiates to other excitatory cells by way of non-NMDA and NMDA glutamatergic ionotropic receptors.[12] This in turn will generate epileptic brain activity.

Seizures progress due to sustained membrane potential depolarization, rhythmically occurring action potentials, and lack of inhibitory control. In the neocortex epileptic activity can propagate through any cortical layer; however, preference is given to layer V.[15] As such, cortico-cortical connections are very important for the spread of seizures to multiple brain regions. Eventually, the membrane potential will hyperpolarize to end a seizure. Once a seizure is terminated, the post-ictal period follows during which there is a relative suppression of neuronal activity that corresponds to clinical symptoms of somnolence, confusion, and weakness, lasting for 15-60 min or longer.

1.4 Classification of Seizures and Epilepsy

Epilepsy classification can be based on many factors, such as seizure etiology, semiology, and/or epileptogenic focus. Epilepsies classified based on etiologies are usually separated into three general categories. Genetic epilepsies are caused directly by a genetic abnormality, which can be either inherited or due to environmental factors.[16] Structural or metabolic epilepsies are the result

of developing epileptic seizures due to another disease. Examples include stroke, trauma and infection.[16] Lastly, idiopathic epilepsies arise in patients without a known or identifiable cause.[16]

Epilepsies classified according to the location of the epileptogenic focus (where the seizures originate within the brain) are categorized as either generalized or focal.[16] Generalized epilepsies are characterized by epileptic seizures that have unclear seizure onset localization and lateralization, both of which can be inconsistent.[16] Seizure types included in this category are tonic-clonic, absence, myoclonic, tonic, clonic, or atonic. Alternatively, focal epileptic seizures have an onset consistently localized to one hemisphere, which can be both discrete or diffuse.[1,16] Despite localized seizure onset zones in focal epilepsies, seizures may become secondarily generalized to encompass the entire brain. Focal epilepsies are further classified depending on the origin of seizure onset, which is generally based on the lobe that the origin resides (e.g., frontal, temporal, parietal, or occipital).[16] Depending on the focal region and area of spread, seizures result in varying degrees of impairment. Seizures without impairment of consciousness can include those that have visible motor, autonomic, sensory, or psychic components. Alternatively, seizures may cause impairment of awareness, or progress from an unimpaired to impaired state.[16]

1.4.1 Frontal Lobe Epilepsy

FLE is the second most common type of focal epilepsy.[17] Many causes of FLE have been identified including neoplasm, vascular insults, trauma, malformations of cortical development, infection, inflammatory disease, metabolic conditions, and systemic causes.[17] Clinical manifestations are very diverse in patients with FLE, however, there are some distinct clinical features of frontal lobe seizures that help distinguish FLE from other epilepsy types. Frontal lobe

seizures generally occur during sleep, cluster together, have early motor manifestations and vocalizations, and can result in complex and hyper-motor activity.[17] While some of these ictal symptoms may also occur during other seizure types, they are more common during frontal lobe seizures.

The locations of frontal lobe seizure foci can be subdivided into the perirolandic or primary motor, supplementary sensorimotor, dorsolateral, orbitofrontal, anterior frontopolar, opercular, and cingulate regions (Figure 1.1).[17]

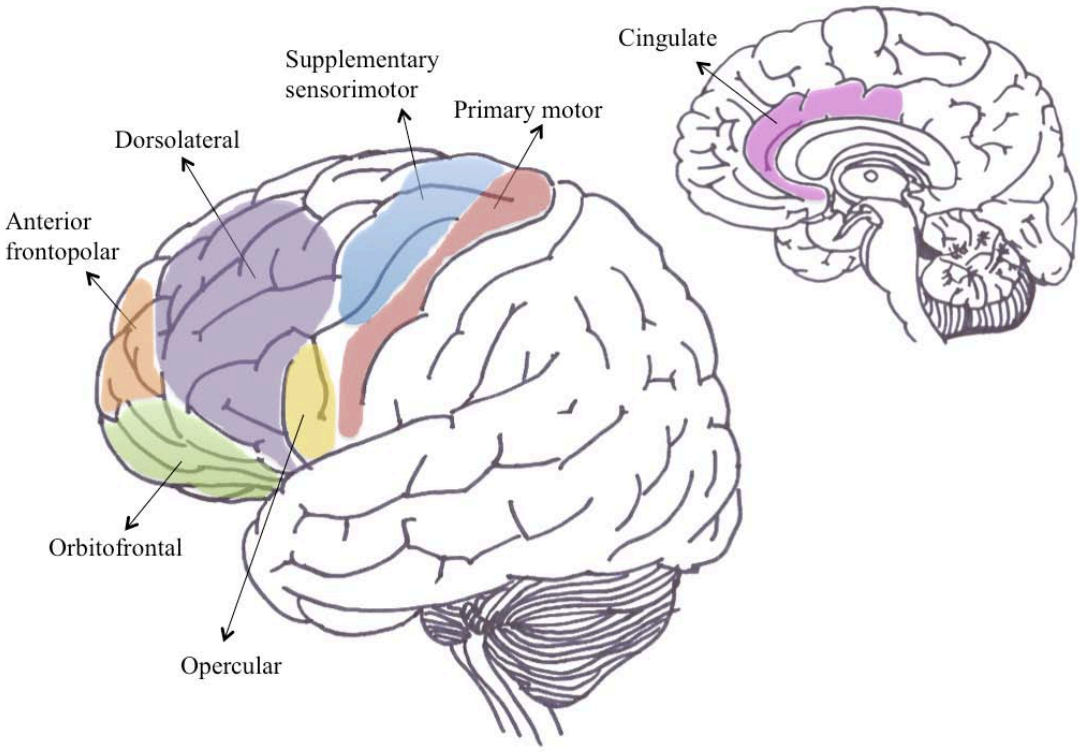


Figure 1.1 Common seizure onset zones in patients with FLE.

Seizures arising from each of these regions have somewhat distinct clinical manifestations. Primary motor seizures generally begin with motor activity in the face region, which is quickly followed by speech arrest; loss of consciousness does not usually occur.[17] Supplementary sensorimotor seizures are characterized by unilateral or bilateral tonic posturing of the limbs;[17] they are usually very brief and speech arrest or vocalization may occur.[17] The remaining five types of frontal lobe seizures are less distinct in their clinical manifestations due to partial regional overlap, making it harder to differentiate seizure foci using ictal symptoms. Dorsolateral seizures are often accompanied by focal tonic or clonic movements, forced head deviation, and speech arrest.[17] Orbitofrontal seizures usually produce behavioural arrest or unresponsiveness and motor automatisms.[17] Anterior frontopolar seizures are characterized by a subtle lapse in consciousness, forced motor movements, and autonomic signs.[17] Chewing, salivation, swallowing, gustatory hallucinations, and other autonomic manifestations may accompany opercular seizures.[17] Lastly, cingulate seizures are characterized by complex motor behaviour, autonomic symptoms, and very emotional experiences.[17]

1.4.1.1 Motor Deficits in Patients with Frontal Lobe Epilepsy

Both clinical and experimental evidence reveals the importance of the frontal lobes in executing motor coordination.[18] Thus, it is not surprising that during the ictal period, some form of positive or negative motor symptom accompanies all types of frontal lobe seizures. However, patients with FLE commonly exhibit motor deficits on a daily basis, suggesting that seizure activity also affects brain function during interictal periods. During neuropsychological testing, impairments have been reported in patients with FLE in cognitive functioning and motor skills (including motor control, coordination, and planning) when compared to healthy controls.[3,7] Patients with

FLE also score significantly lower compared to patients with TLE when evaluated on tasks that measure psychomotor speed, attention, coordination, motor planning, and motor sequencing.[7] Motor dexterity was found to be a salient distinguishing feature when comparing these two groups.[19] Despite these differences, patients with TLE and FLE could not be distinguished based on their performance in measures assessing intelligence, memory, executive functions, and emotional conceptualization, only that both of these groups demonstrated significant impairments when compared to controls.[7] These findings highlight the importance of investigating cortical motor function in patients with FLE.

Concordant with observations in humans, rats have also been shown to experience motor deficits after being exposed to repeated seizure-like activity.[20,21] These deficits include impairments in reaching, grasping and walking across horizontal surfaces.[20,21] These studies are important because they occur under experimental conditions where many confounding variables have been removed, such as the effects of anti-seizure medication and individual differences in seizure characteristics.[20] It is then possible to more accurately determine whether motor deficits are the result of frontal lobe seizures, or other external factors.[20]

1.5 Clinical Approaches to the Diagnosis of Epilepsy

When a patient seeks medical attention after presentation of one or several seizures, a thorough medical history is taken. This includes a detailed description of the events prior to, during, and after the seizure as recalled by both the patient and witnesses. Family medical history can also be a critical step in the diagnosis of epilepsy due to possible risk factors such other family members with epilepsy. Following this examination, patients will generally proceed with two main neurological investigations: EEG and structural MRI.

1.5.1 Electroencephalography (EEG)

EEG works on the basis of temporally summed voltage fluctuations that occur in cortical pyramidal cells. These voltages can be detected by electrodes placed on the scalp or directly on the cortical surface, known as intracranial EEG.[22] Distinct waveforms are generated during ictal and interictal periods, which are used to identify the occurrence of epileptic seizures, frequency of seizures, and precise location of where the seizures begin (i.e., the seizure focus) in an individual.[22] EEG is a useful technique due to its high temporal resolution; however, this is at the expense of lower spatial resolution (>10 cm^2).[23] Continuous video monitoring is often performed concordantly with EEG recordings to allow for direct comparison between electrophysiological information and clinical manifestations during a seizure. This technique, which can further aid in the identification of a seizure focus, is known as video-EEG monitoring (VEM).

Frontal lobe seizures are often identified using scalp EEG. However, seizures may not always be associated with clear EEG changes due to movement artefact, deep seizure foci, etc. Furthermore, while interictal discharges occur in 60-80% of FLE patients, they can be bilateral, multilobar, or generalized, thus limiting their usefulness in localizing the seizure focus.[22,24] Also, surface electrodes cannot detect deep cortical areas within the frontal lobe, and activity detected by electrodes may be due to propagation.[17,24] As a result, scalp EEG can identify a seizure focus in only 33% of patients with FLE.[24]

1.5.2 Structural Magnetic Resonance Imaging (MRI)

MRI is a mainstay in the investigation of patients with epilepsy. It is advantageous due to its high spatial resolution, non-invasiveness, and lack of ionizing radiation. MRI uses the property of nuclear magnetic resonance (NMR) to image specific atomic nuclei within the body. Hydrogen is

the most common atom to image due the body's high water content, and it is serendipitously the most sensitive to the NMR phenomenon. The strong magnetic field of an MR scanner causes NMR-sensitive nuclei to align in the direction (either parallel or anti-parallel) of the magnetic field; this is because the nuclei themselves are tiny magnets as a result of their net electric charge and spinning nature. Additional briefly applied magnetic fields (often called radio frequency pulses) are used to disturb the equilibrium of this alignment. Once these fields are removed, the nuclei return to their equilibrium alignment, generating a decaying radio frequency signal that is recordable. Since different tissues types have distinct water contents and chemical and magnetic environments (e.g., grey matter, white matter, CSF), nuclei return to equilibrium at differing rates and the signals they generate decay at differing rates. These processes are characterized by tissue specific decay constants, T1 and T2, respectively, and generate tissue contrast on an MR image depending on which mechanism the timing parameters of the image acquisition are set to exploit (i.e., T1-weighted or T2-weighted). These properties are important for the identification of structural abnormalities in patients with epilepsy to determine a potential epileptogenic source. Abnormal findings in patients with FLE commonly include tumors, lesions due to trauma, cavernous malformations, malformations of cortical development, and gliosis (Figure 1.2).[25] Successful surgical outcome in patients with FLE is significantly correlated to pathological abnormalities identified using MRI.[25] The majority of patients with FLE, however, have reportedly normal MR scans,[25] thus complicating their clinical management.

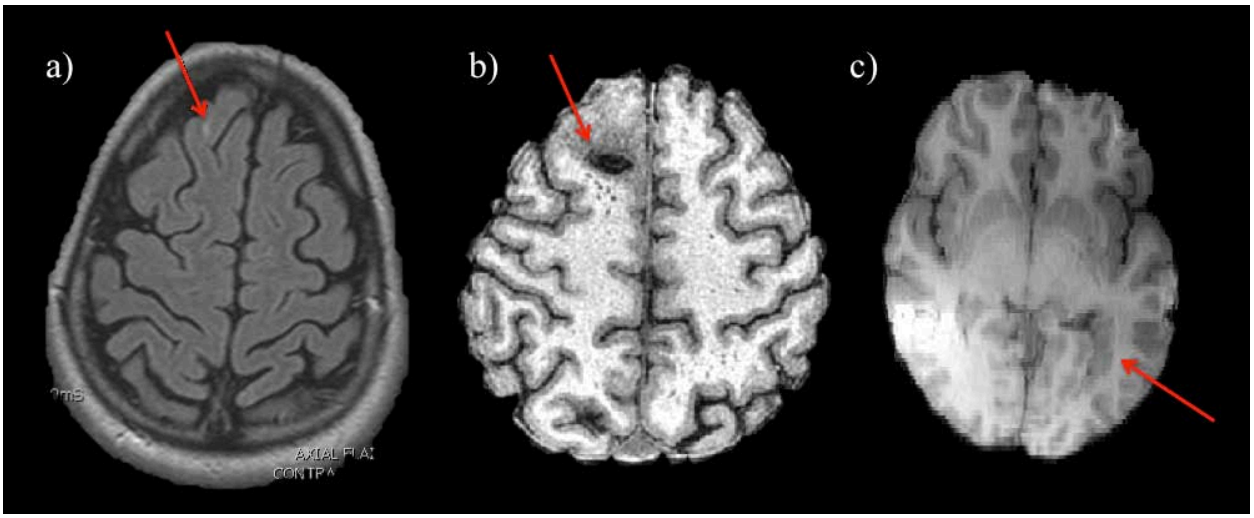


Figure 1.2 Examples of abnormal MR scans in patients with epilepsy: a) cortical dysplasia, b) cavernous angioma, and c) periventricular heterotopia.

1.6 Clinical Approaches to the Management and Treatment of Epilepsy

1.6.1 Anti-Epileptic Drugs (AEDs)

Currently, the first treatment option for seizure management in patients with epilepsy is anti-epileptic drugs (AEDs). The type of AED or combination of AEDs used for an individual primarily depends on seizure type or epilepsy syndrome, but other influential factors include pharmokinetics, side effects, dosing interval, cost, and availability.[26] AEDs primarily reduce seizure frequency by decreasing excitatory or increasing inhibitory neural activity.[26] Mechanisms of action include targeting GABA by preventing its breakdown or increasing the inhibiting action of $GABA_A$ receptors, increasing inactivation of sodium channels to reduce consistent high-frequency action potentials, or decreasing T-type calcium channel currents.[26] Seizures with partial onset, including secondary generalization, can generally be treated using any conventional AED.[26] Commonly, the effects of several AEDs need to be combined in order to decrease seizure

frequency. Unfortunately, seizure reduction or elimination is not achievable for approximately 20-30% of patients through AEDs.[27] Drug resistance can be due to many factors; however, it is estimated that approximately 60% of all drug resistant cases occur in patients with focal epilepsy, including patients with FLE.[27]

1.6.2 Surgery

Surgery is considered when AEDs fail to adequately control seizure frequency and severity, and if it is probable that surgery will reduce the occurrence of seizures thereby improving a patient's quality of life.

1.6.2.1 Pre-Surgical Investigations

First, it is important to conduct an extensive pre-surgical evaluation to determine the most advantageous surgical procedure for the patient. Pre-surgical investigations include video, scalp, and intracranial EEG, MRI, single-photon emission computed tomography (SPECT), positron emission tomography (PET), and neuropsychological assessment. As discussed previously, video-EEG monitoring is used to correlate clinical manifestations with electrophysiological events in order to identify one or multiple seizure foci, and structural MR imaging is used to identify structural abnormalities that may correlate with epileptic EEG activity.

Ictal SPECT uses a gamma-emitting radio-ligand that is injected into the patient's bloodstream at ictal onset. The radio-ligand travels through the bloodstream to the region of interest, where the radioisotope decays and emits gamma rays that can be seen using a gamma-camera. Iodine-123 and technetium-99m-labeled radiopharmaceuticals are typically used because of their ability to cross the blood-brain barrier quickly, and remain in the tissue for more

than 30 minutes so that a relatively accurate image can be taken.[28] Ictal SPECT is used based on the assumption that increased neuronal activity at the seizure focus will be associated with increased metabolism, therefore causing increased cerebral blood flow to that area via cerebral autoregulation.[28] Interictal SPECT is also performed, as seizure foci may exhibit hypo-perfusion during the time between seizures. Both interictal and ictal SPECT are often acquired in the same patient; subtraction of the interictal and ictal images is more sensitive than the interictal or ictal SPECT methods alone. Co-registration of the SPECT data with structural MR data is performed to more precisely localize any abnormalities observed by SPECT.

PET is similar to SPECT in that a radioligand is injected intravenously. Fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) is used in PET to measure brain metabolism rather than cerebral blood flow.[28] [^{18}F]FDG is a glucose analog, and therefore an indirect marker of neuronal activity. The epileptic focus will generally appear hypo-metabolic during an interictal scan, and hyper-metabolic during an ictal scan.[28]

Neuropsychological evaluations provide an assessment of sensory, cognitive and motor impairment prior to surgery, and may help to predict the occurrence of post-surgical functional deficits. Areas tested include attention, nonverbal cognitive functions (visual perception, spatial ability, construction skills, auditory perception), executive functions (attention, fluency, memory, planning, concept formation, social behaviour), language, and sensory and motor functions.[29]

1.6.2.1.1 Cortical Mapping

Cortical mapping is another imperative pre-surgical technique used when resecting specific foci. It is done in order to avoid resecting eloquent cortex (cortex that will result in severe functional deficits if removed) in patients that have seizure foci in critical areas (e.g., motor cortex in

patients with FLE). Cortical mapping can be performed using direct cortical stimulation, magnetoencephalography, transcranial magnetic stimulation, or task-based fMRI.

Direct cortical stimulation is currently the gold standard for mapping the motor cortex in individual patients.[30] Areas of the primary motor cortex are exposed and stimulated during surgery, while compound muscle action potentials are recorded in contralateral muscles in the face and extremities.[30] Direct cortical stimulation is advantageous over other mapping techniques because it provides the surgeon with real-time feedback about cortical motor areas that should be avoided during resection.[30] However, one disadvantage is resultant after-discharges that may initiate seizures due to the high stimulation intensity that is sometimes required.[30] Provoked seizures can occur in up to 29% of patients undergoing cortical stimulation.[30]

Magnetoencephalography is a noninvasive technique that records magnetic fields generated by electrical currents within the brain.[30] Previous studies have shown that voluntary movements are associated with event-related desynchronization in the beta-frequency band (~12-30Hz).[30] Therefore, this desynchronization is indicative of cortical areas involved in motor output. Magnetoencephalography has proven to be a valid presurgical technique for motor cortex mapping when compared to cortical stimulation.[24]

Transcranial magnetic stimulation is also a noninvasive technique used for pre-surgical motor mapping. A device that generates a rapidly changing magnetic field is placed on the participant's head over the vicinity of the motor cortex. This field induces an action potential in groups of neurons, specifically pyramidal neurons in the primary motor cortex. Resultant movements in the corresponding muscle groups can be detected using electromyography.[30]

FMRI acquired during the performance of motor tasks produces cortical motor maps that have excellent concordance with magnetoencephalography, transcranial magnetic stimulation,

and direct cortical stimulation.[31] Studies have reported up to 100% agreement between fMRI and cortical stimulation results when mapping cortical motor areas.[31] This concordance has led to the contribution of fMRI to surgical management in up to 74% of patients studied, depending on the centre.[24] Contributions include determining the specific surgical procedure/approach to be pursued, benefit-risk ratio assessment, and determining whether or not to perform surgery.[24] FMRI will be further discussed in section 1.8.

1.6.2.2 Surgical Procedures in Epilepsy

Following these extensive pre-surgical investigations, physicians must determine the best surgical option for managing seizure frequency and severity. Surgical procedures considered in epilepsy include temporal resections, extratemporal resections, hemispherectomies, multiple subpial transections, and corpus callosotomies.[32] During surgical resections, cortical tissue thought to be involved in seizure generation is removed, while leaving behind as much eloquent tissue as possible. Temporal resections are one of the most commonly performed epilepsy surgeries due to the high prevalence of TLE. These resective surgeries generally include removal of anterior and mesial temporal structures, or a complete anterior temporal lobectomy depending on the postulated seizure focus.[32] Extratemporal resections are less common because of a lower prevalence of extratemporal epilepsies. It can be quite difficult to define a resection margin in these regions in order to limit post-surgical functional deficits. If the epileptic focus lies in functionally essential cortex, the surgeon may perform multiple subpial transections. Horizontal connections are broken within epileptic tissue in the grey matter in attempt to stop seizure propagation and maintain functionality.[32]

Patients with generalized epilepsies may have multiple seizure types and no clear foci, rendering them ineligible for resection or multiple subpial transections. Another option is to perform a corpus callosotomy, where the two hemispheres are disconnected to stop inter-hemispheric seizure propagation, therefore making the patient's seizures less disabling.[32] A hemispherectomy is a palliative procedure considered primarily in children with severe hemiparesis and extremely disabling seizures localized to one hemisphere.[32] Hemispherectomies can be fatal and have been widely replaced by functional hemispherectomies. This involves widespread dissection of white matter tracts in the affected hemisphere in order to disconnect it from the healthy hemisphere, thus leaving critical regions in the affected hemisphere intact.[32]

The surgical outcome of patients with FLE is less favourable than the more common TLE, with studies reporting between 30-50% of patients achieving post-surgical seizure freedom.[17] The reason for surgical failure in FLE, as in other epilepsies, is incomplete or inaccurate identification of seizure foci. FLE in particular is often characterized by clinical manifestations that can be difficult to interpret, a lack of localizable EEG changes during seizures, and MR scans that do not show a clear lesion. Even if the epileptogenic focus is precisely located many areas of the frontal lobe have critical functions, including the motor cortex, and in order to maintain functionality surgeons are unable to perform a complete resection of the seizure focus.

1.7 Motor Networks

The first identified cortical motor regions included the precentral (Brodmann Area 4, BA4) and intermediate precentral (BA6) cortex. BA4 constitutes the primary motor cortex, and BA6 includes the premotor and supplementary motor cortex; all three cortical regions were thought to be functionally distinct. This model has since become more complex to further elucidate motor regions and include cortex external to BA4 and 6, while recognizing these areas are not functionally distinct (Figure 1.3). Regions are defined based on cytoarchitecture, myeloarchitecture, metabolic architecture, connectivity, and receptor mapping.

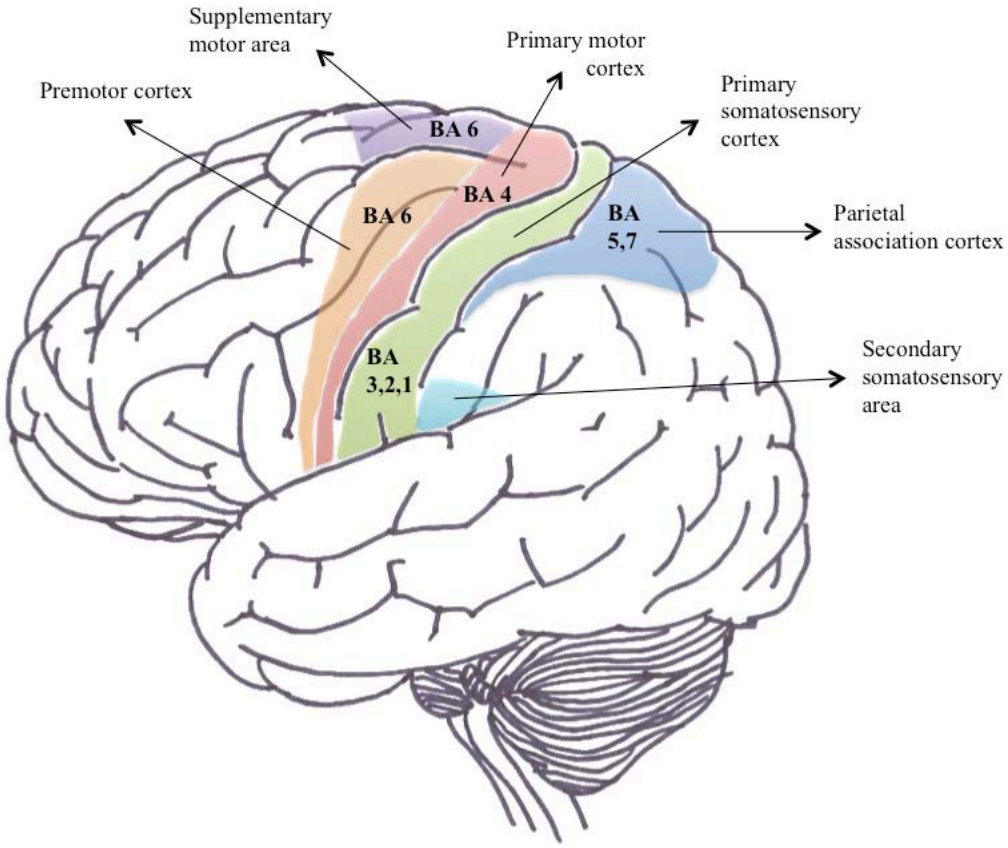


Figure 1.3 Major cortical brain regions involved in motor output.

The primary motor cortex can be characterized by the 'motor homunculus'; a representation of discrete cortical regions that directly influence individual body parts. It is now thought that there is more overlap within these regions and that a one-to-one interaction between distinct cortical regions and the voluntary movement of body parts does not exist. The primary motor cortex is molecularly unique in its lack of granule cells in layer IV and presence of many giant Betz cells (type of pyramidal neuron) in layer V (Figure 1.4).

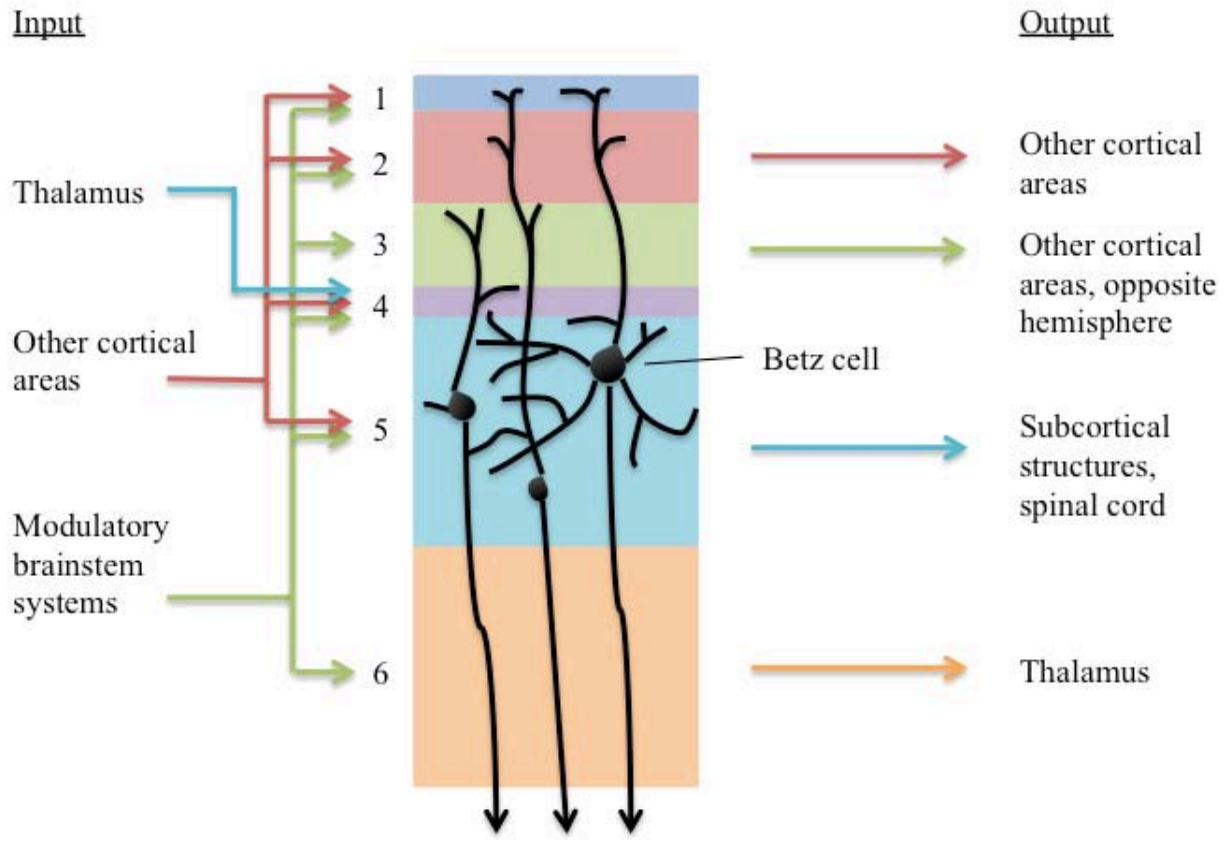


Figure 1.4 Cortical layers of the motor cortex.

Betz cells account for approximately 3% of the neurons projecting from the primary motor cortex to the spinal cord,[33] whereas the remaining projections come from other layer V pyramidal cells. The primary motor cortex primarily receives input from the thalamus, cingulate cortex, parietal cortex, supplementary motor cortex, and premotor cortex.

The thalamus serves as the main relay center for the cortex, and primarily relays motor information to the primary motor cortex from the basal ganglia and cerebellum. Three types of nuclei are present in the thalamus: the anterior, medial, and lateral nuclei. The motor system relies primarily on the lateral nuclei, in which there are dense connections with many motor regions, including the cingulate motor area. This cingulate region receives input from thalamic nuclei, and in turn generates two-way feedback with the primary motor and parietal cortex. The posterior parietal cortex serves as an integration center by receiving sensory input from the visual, auditory, and somatosensory system.[34] This information is later sent to regions such as the supplementary motor area to assist in the planning of motor functions. The supplementary motor area is more specifically involved in the direct control of *complex* movement, including movements that occur in sequences or require coordination, and generating internally conceptualized movements. Important cortico-cortical connections exist between the supplementary motor area and primary motor cortex; however, outputs from the supplementary motor area also contribute significantly to the corticospinal tract. Similarly, the premotor cortex has a reciprocal interaction with the primary motor cortex, as well as the supplementary motor area and superior and inferior parietal cortex, and sends projections to the spinal cord. Functional roles of the premotor cortex include participating in the spatial and sensory guidance of movement, including guided reaching and grasping tasks, and associating sensory stimuli with specific motor tasks.[35] As mentioned previously, the supplementary motor cortex and premotor

cortex contain many dense connections within and between them, allowing for bidirectional information transfer. Both of these regions receive input directly from the prefrontal cortex,[36,37] which is involved in the most complex motor planning, organization, and regulatory motor functions.[37]

The cerebellum is an important brain region that assists in various motor functions including coordination, precision, and timing. It receives input from both cerebral cortex and spinal cord in order to fine tune motor control.[36] Anatomically, it consists of an outer cerebellar cortex, with a set of small deep cerebellar nuclei imbedded in the underlying white matter. The cerebellar cortex is divided into the vestibulocerebellum, spinocerebellum, and cerebrocerebellum, the functions of which are listed in the table below (Table 1.1).

Table 1.1 Divisions of the cerebellar cortex including regions from which input is received and overall function.

Cerebellar Division	Input	Function
Vestibulocerebellum	Semicircular canals, vestibular nuclei, superior colliculi, visual cortex via pontine nuclei	Helps control balance and eye movements
Spinocerebellum	Dorsal columns of spinal cord, trigeminal nerve, visual and auditory systems	Regulates body and limb movements
Cerebrocerebellum	Primary motor cortex, somatosensory cortex, supplementary motor area, premotor cortex and posterior parietal cortex, all via pontine nuclei	Integrating sensory information in order to plan future movements

The cerebellum connects extensively with cerebral motor areas to assist with various aspects of movement, motion perception, and motor learning.[38] Cerebellar damage most commonly results in impairments in balance, involuntary jerks, unsteady walking, and gait ataxia.[38,39]

The basal ganglia are a collection of tightly interconnected nuclei positioned deeply within the cerebrum. The putamen and caudate, or neostriatum, receive extensive input from the cortex; the primary motor and sensory cortex send information to the putamen, and the frontal and parietal association areas send information to the caudate. These regions pass information between all basal ganglia nuclei including the globus pallidus, substantia nigra, and subthalamic nuclei in order to initiate and regulate motor commands. The basal ganglia have also been implicated in learning motor sequences and reward learning.[39] If the basal ganglia are functionally disrupted in some way, people generally experience impairments including tremor, chorea, bradykinesia, akinesia, and changes in muscle tone.[39]

The brain sends motor information to the rest of the body via descending spinal cord tracts. Two main groups of tracts exist; i) pyramidal, which send information directly to the spinal cord without any synaptic interruption, and ii) extrapyramidal, which form synapses with subcortical structures before proceeding to the spinal cord.

The corticospinal tract is considered to be the major pathway for skilled movements; however, only 55% of its fibres come from primary and secondary motor cortex (BA 4 and 6).[40] About 35% come from the somatosensory cortex (BA 3, 2 and 1), and the remaining 10% originate in other frontal and parietal regions.[40] The tract is comprised of axons from layer V neurons, which terminate in all layers of the spinal cord grey matter. Most of these axons form synapses with interneurons, but they also synapse onto lower motor neurons. In fact, a majority of axons from the primary motor cortex (particularly in the hand region) make monosynaptic connections directly onto spinal cord motor neurons. These monosynaptic connections are thought to facilitate more refined motor control.[41] A summary of other major descending motor tracts is listed in Table 1.2.

Table 1.2 Major descending motor tracts in the spinal cord

Tract	Origin	Termination	Function
Lateral cortico-spinal	Primary motor and other frontal and parietal areas	Entire cord (mainly cervical and lumbosacral)	Movement of contralateral limbs [42]
Anterior cortico-spinal	Primary motor and supplementary motor area	Cervical and upper thoracic cord	Control of bilateral axial and girdle muscles [42]
Cortico-bulbar	Ventral motor cortex and supplementary motor area	Brainstem nuclei	Conscious control over eye, jaw, and face muscles [40]
Cortico-rubral	Sensorimotor cortices	Red nuclei; gives rise to **rubrospinal** tract	Fine motor Coordination [42]
Cortico-reticular	Sensorimotor cortices	Pontine and medullary reticular nuclei; gives rise to **reticulospinal** tract	Posture, gross motor coordination, balance [40]
Cortico-tectal	Occipital and inferior parietal cortices	Superior colliculi; gives rise to **tectobulbar** and **tectospinal** tracts	Coordination of head and eye movements [42]
Medial and lateral vesibulo-spinal	Medial and inferior vestibular nuclei	Medial: cervical and upper thoracic cord Lateral: entire cord	Medial: Positioning of head and neck Lateral: balance [40]

1.8 Functional Magnetic Resonance Imaging (fMRI)

FMRI is a method that can be used to examine motor networks and brain function. It is a non-invasive technique that has no known identified risks. Evoked neuronal activity is an aerobic process, necessitating an increase in the delivery of oxygenated blood to the neuronal sites that require it. This is accomplished by an increase in local blood flow, which is directly correlated with neural activity via a cerebral autoregulation mechanism known as the hemodynamic response (HDR). The MR signal is sensitive to blood oxygenation; the paramagnetic properties of deoxygenated hemoglobin interfere with the MR signal, causing local magnetic field

inhomogeneities and therefore loss of signal. Consequently, decreased deoxygenated hemoglobin levels as a result of increased blood flow result in a greater MR signal. This provides a temporal contrast when neural activity levels are modulated. This mechanism is called Blood Oxygen Level Dependent (BOLD) contrast.[43]

More specifically, before a stimulus occurs to evoke neural activity oxygenated and deoxygenated hemoglobin are at baseline levels in surrounding blood vessels. Upon presentation of a stimulus glutamate is released causing activation of NMDA and AMPA receptors on surrounding astrocytes.[44] This increases the intracellular calcium concentration, which activates nitric oxide synthase to produce nitric oxide, which can then diffuse outward.[44] Nitric oxide is a vasodilator and causes arteries to expand and increase blood flow. This initial process takes approximately two seconds to complete, hence there is a lag in the HDR.[44] During this lag period neurons still require increased oxygen and consume it from the surrounding vessels. This causes the concentration of oxygenated hemoglobin to decrease, but more importantly the deoxygenated hemoglobin concentration to increase, resulting in a slight distortion of the MR signal and an initial undershoot in the observed BOLD signal.[44,45] Once this lag period is over and blood flow increases, there is a corresponding increase in oxygenated hemoglobin and decrease in deoxygenated hemoglobin, which results in a BOLD signal increase.[44] The BOLD signal peaks at approximately 5 seconds following a neural stimulus.[44] Since response to a stimulus is a transient event the active tissue slowly depletes the source of oxygenated hemoglobin as blood flow returns to normal.[45] This causes the BOLD signal to decrease towards baseline. However, an undershoot occurs; this is because of a return to normal blood flow, but slow cerebral blood volume recovery.[44] Deoxygenated hemoglobin produced due to neural tissue activity diffuses into the surrounding vessels. These vessels can still accommodate more than baseline due to their

increased volume, but not flush away excess because they have returned to normal flow rates. Once both cerebral blood flow and volume return to baseline, deoxygenated hemoglobin concentrations also normalize and as a result the BOLD signal does as well.[44] This entire relationship can be represented by the hemodynamic response function (Figure 1.5). The amplitude of the BOLD signal has been shown to vary across individuals and brain regions.[44]

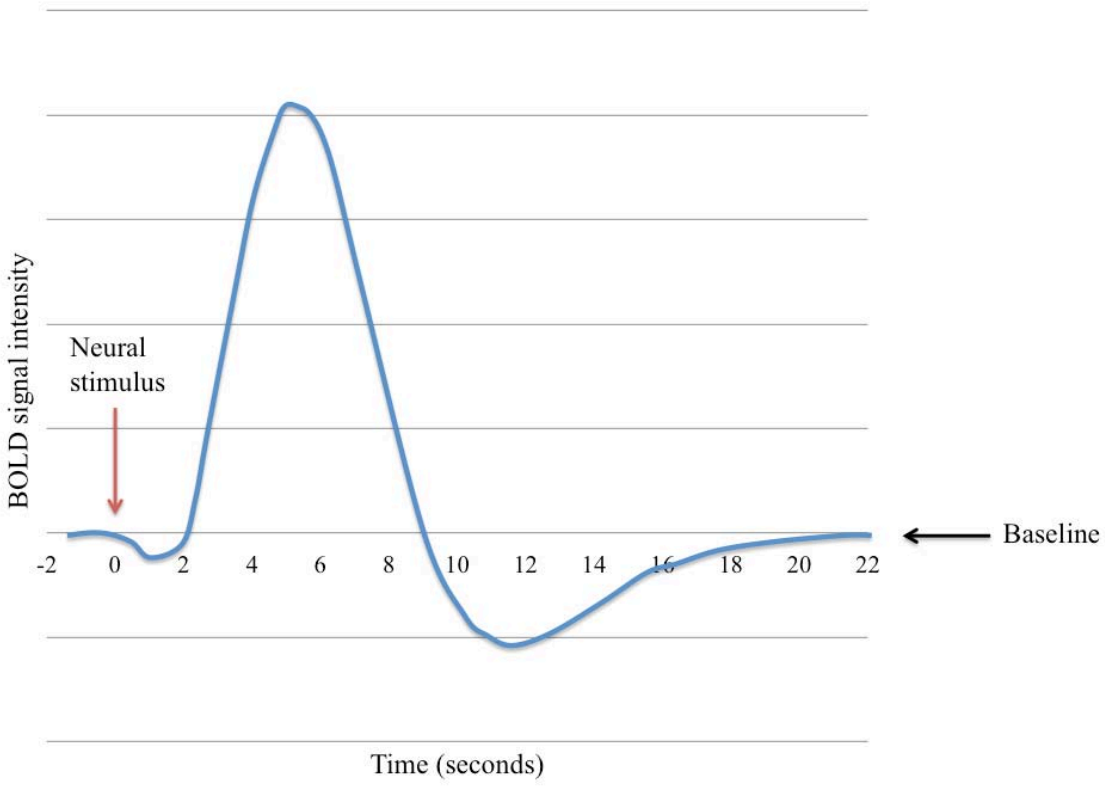


Figure 1.5 Example of a typical hemodynamic response to a brief neural stimulus.

1.9 Cortical Plasticity

Current research demonstrates the ability of functional organization in the cortex to change in response to behaviours, environment, and injury, after the developmental period is over. This

phenomenon is known as cortical plasticity. Profound changes in cortical organization have been reported in a variety of neurological diseases or injuries, including Parkinson's disease,[46] amyotrophic lateral sclerosis,[47] stroke,[48] and brain trauma,[49] just to name a few.

During cortical development, processes such as axon growth, synapse formation, synaptic pruning, and synaptic strengthening allow for normal brain development. At the end of the critical neural development period these processes are altered slightly to provide stability in the adult brain, yet still allow for functional changes to occur.[50] Two of the foremost processes that persist into adulthood to allow for synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD). These mechanisms strengthen and weaken synapses between neurons, respectively, and are stimulated by the frequency of synaptic use as well as in response to injury.[50] Changes in synaptic strength can lead to modifications in response threshold to excitatory and inhibitory synaptic potentials;[51] however, over time the formation of new synapses and removal of unused synapses can lead to overall alterations in cortical maps.[51]

1.9.1 Cortical Plasticity in Epilepsy

Seizures can alter normal developmental processes in the cortex, as well as induce cortical changes in adult life. This implies that age at epilepsy onset may affect cortical motor organization. Early seizure onset, which occurs during normal cortical development, may lead to abnormal development of functional organization.[52] However, because the critical period has not yet ended, the brain may be able to make compensatory changes by reallocating cortical function to counteract any deficits.[52] Children with seizures beginning during this period may experience fewer motor deficits than those with seizures beginning later.[52] Alternatively, if disruption of normal cortical development occurs early in life and this disruption is repetitive, such as

recurrent seizure activity, this can render the brain unable to make any *functionally beneficial* compensatory changes.[53] As such, children with early onset epilepsy have also been shown to perform worse on functional tasks.[53]

When seizure onset occurs later in life the brain continues its attempts to induce cortical changes in order to compensate for functional impairments. Functional cortical changes have been well documented in patients with TLE. Cortico-cortical evoked potentials have been used to evaluate functional language regions and determine connectivity between Broca's and Wernicke's area.[54] Language areas were found to extend beyond the classical representations to include parts of the rolandic and sylvian fissues, angular gyrus, and temporo-occipital junction.[54] A change in the connectivity between Broca's and Wenicke's area was also observed.[54] Similarly, fMRI studies conducted by our group demonstrated that patients with TLE exhibit differences in functional activation compared to control subjects when performing language tasks, in association with poorer performance.[5,55] Not only is functional language organization different in patients with TLE compared to controls, but visual memory also exhibits different activation patterns. A study of patients with right TLE showed increases in activation of the left hippocampus as opposed to the right hippocampus (right hippocampus activation is typically observed in controls), as a means to preserve visual memory.[56]

1.9.2 Cortical Plasticity in the Motor Cortex

Cortical plasticity also occurs in cortical motor regions in patients with epilepsy. One study examined patients with epileptic foci in sensory or motor regions using transcranial magnetic stimulation.[57] Using this technique, researchers determined a shift in the cortical area representing the right and left abductor pollicis brevis (APB) muscles.[57] They also determined a

greater difference between map size of the left and right APB, depending on the epileptic focus.[57] Transcranial magnetic stimulation has additionally been used to examine motor cortex excitability in patients with seizure foci outside of the primary motor area. Specifically, motor cortex ipsilateral to the seizure focus exhibited increased excitability and decreased inhibition when compared to the contralateral cortex, suggesting that seizure propagation can impact distant cortical function.[58] Both of these studies demonstrate the functional changes that seizures can induce on the organization of the motor cortex, even when they originate in distant sites. It can also be noted that changes in organization differ depending on the hemisphere containing the seizure focus,[57,58] providing insights into the effects of intra-hemispheric versus inter-hemisphere seizure propagation.

Other studies have noted trends in reallocation of motor function to other cortical sites. One PET study of patients with unilateral rolandic cortex lesions demonstrated increased contralesional rolandic cortex activity as well as increased involvement of secondary motor and frontoparietal cortices.[59] Other PET and transcranial magnetic stimulation studies have observed similar results: post hemispherectomy when cortical motor regions are forced to reorganize to the contralateral hemisphere, motor function is *not* transferred to the primary motor cortex but to other nearby motor regions.[60] This perhaps suggests that motor regions outside of the primary motor cortex are more responsive to changes in functional organization.

Cortical motor plasticity has been studied in patients with seizure foci in motor regions, however no research has been conducted with a group of patients with FLE specifically using fMRI, one of the least invasive techniques. More importantly, fMRI provides cortical maps with higher spatial resolution than any other currently available non-invasive technique. Research examining cortical plasticity in functionally critical brain regions highlights the importance of

performing thorough pre-surgical investigations in an effort to minimize the removal of brain tissue critical to a specific function (e.g., language, motor, memory).

1.9.3 Cortical Plasticity in Animal Models of Epilepsy

The kindling model of epilepsy is one method that can be applied to animals in order to study the affect of seizures on the brain. Initially, low-intensity electrical stimulation is applied to a specific area of the brain, generally resulting in little behavioural change.[61] However, after repetitive low-intensity stimulation behavioural changes become apparent and eventually result in bilateral clonic convulsions.[61] These changes have been shown to occur due to propagation of electrical activity.[61] Overall, increased kindling results in increased duration and severity of seizures. These effects are long lasting and occur due to changes in the organization of cortical connections.[61]

Studies conducted in rats have demonstrated that cortical motor representations of the forelimb respond to a lower threshold of stimulation following kindling of the hippocampus, corpus callosum, and amygdala.[62,63] Additionally, cortical regions that did not previously produce motor movements in response to electrical stimulation did following kindling.[62,63] These results suggest a revealing of the full motor representation in the brain. Motor map revealing was observed concurrently with changes in motor behaviours.[20,63] These experiments provide important findings; researchers are able to study the effects of seizures on cortical plasticity without the presence of confounding variables, such as AED combinations or environmental influences that occur in humans.

1.10 Resting-State Connectivity

The cortical changes discussed above have been demonstrated in terms of functional activation in response to external stimuli. However, changes in intrinsic cortical networks have also been demonstrated.[64,116] FMRI has the potential to investigate these networks and has demonstrated slow (<0.1Hz), spontaneous fluctuations in the BOLD signal during rest. These fluctuations are temporally correlated between functionally related brain regions (e.g., motor, visual, etc.) and represent the energy-demanding intrinsic signalling that occurs between brain regions at rest, hence the term resting-state connectivity.[66] However, these intrinsic networks have also been demonstrated during task performance, while under sedation, during sleep, during all stages of development, and in all species of animals that have been studied thus far.[67] Little is known about the physiological origin of intrinsic communication at rest; however, its high energy demands imply it is most likely a critical phenomenon. Current theories suggest it may be responsible for developing and maintaining neural networks that function in response to external stimuli, as well as increasing efficiency and ensuring the reliability of these networks.[68]

1.10.1 Resting-State Connectivity in Epilepsy

It is generally recognized that a decrease in resting-state connectivity between two brain regions indicates a network disruption, whereas increased connectivity implies recruitment of alternative resources as a mode of compensation.[69] Previous studies have demonstrated altered connectivity networks in patients with epilepsy and have hypothesized that these differences may cause the patient to experience specific functional deficits. For example, patients with left TLE demonstrate significantly lower connectivity between language areas compared to controls, potentially explaining the language impairments that they commonly experience.[6] Another study

examining patients with left mesial TLE determined that there was a reduction in connectivity of both the left and right hippocampus to other brain regions, including the angular gyrus, precuneus, right thalamus, medial and superior frontal gyri, and posterior cingulate.[70] The degree of decreased connectivity between the left hippocampus and medial frontal cortex was positively correlated with decreased memory task performance.[70] Both of these studies suggest a relationship between decreased connectivity within specific networks and functional deficits.

Patients with epilepsy have also demonstrated modifications in resting-state *motor* networks. Two distinct studies focusing on patients with idiopathic generalized epilepsy and children with juvenile myoclonic epilepsy both found altered motor networks in patient groups when compared to controls.[71,72] More specifically, one study reported increased resting-state connectivity between motor and premotor areas in patients with idiopathic generalized epilepsy; this hyper-connectivity correlated positively with years since epilepsy diagnosis.[72] The other study utilized task-based fMRI, focusing on the connections between motor regions.[71] Children with juvenile myoclonic epilepsy had increased connectivity within the motor system (primary motor cortex and supplementary motor area) while performing a highly demanding cognitive task.[71] These results give a possible explanation for the typical myoclonic jerk that these children experience during cognitively stressful situations.[71]

During normal development the brain shifts from having many small isolated networks, to having greater whole-brain connectivity.[74] In fact, recent research has demonstrated that more complex cognitive functions occur due to interactions between various brain regions, instead of small isolated networks.[75] A study using graph theory demonstrated that the frontal lobe functions more as a separate entity in children with FLE when compared to healthy controls.[73] In other words, the frontal lobe had an increased number of connections within it, but a decrease in

the number of connections to the rest of the brain. The extent of frontal lobe isolation was positively correlated with the degree of cognitive impairment.[73]

1.10.2 Clinical Applications of Resting-State Connectivity

Preliminary studies have been conducted in attempt to find clinical applications for resting-state connectivity, including seizure focus localization and predicting post-surgical outcomes.

One study was able to retrospectively identify right vs left mesial TLE purely by examining whole-brain resting-state connectivity with respect to five regions involved in epileptogenic networks of mesial TLE.[76] By determining which hemisphere demonstrated increased connectivity and which hemisphere demonstrated decreased connectivity to the five regions of interest, they could predict a left or right mesial TLE diagnosis at an *individual level* with 64% sensitivity and 91% specificity.[76]

Preliminary research has also been conducted to retrospectively predict functional deficits post-surgery. Patients with both left and right mesial TLE showed connectivity changes that were correlated with post-surgical memory decline; greater connectivity between the posterior cingulate and epileptogenic hippocampus and decreased connectivity between the posterior cingulate and non-epileptogenic hippocampus resulted in a greater reduction in post-surgical memory function when compared to pre-surgical performance.[77]

By examining the resting-state BOLD signal, differences in functional networks between the brains of patients with epilepsy and healthy controls may be discovered, which may ultimately aid in diagnosis, prediction of surgical outcome, and determination of functional deficits.

1.11 Summary

Patients with FLE commonly experience motor impairments during their daily activities.[3,7] Research has demonstrated that functional motor regions in the brains of patients with FLE can be different from locations observed in healthy controls. In other epilepsy groups, such as TLE, changes in the location of cortical regions correlate positively with worse performance scores on tasks measuring the function of said regions. Therefore, one aim of this study was to address whether changes in cortical organization of motor regions could be detected using fMRI in patients with FLE, and whether these organizational changes were accompanied by motor deficits.

Other research efforts have demonstrated differences in the communication between brain regions during rest, and the extent of these differences was positively correlated with seizure burden factors (e.g., years since epilepsy diagnosis). The second aim of this study was to determine whether differences occur in resting-state motor networks in patients with FLE, and whether these differences were correlated with seizure burden factors.

Currently, the source of functional motor deficits in patients with FLE is unknown. Findings from this project may lead to a better understanding of the mechanisms underlying these functional deficits, and ultimately lead to better treatment and recovery options. Additionally, this research may ultimately guide subsequent studies to assist in localization of FLE seizure onset, lead to more informed pre-surgical decisions about the resection site, and predict post-surgical motor function.

1.12 Overall Hypothesis

Patients with seizure activity in the frontal lobe will demonstrate functional changes in the organization of motor regions in the brain, as well as changes in connectivity within motor networks.

1.12.1 Specific Hypothesis 1

Participants with FLE will exhibit greater activity in motor regions contralateral to the seizure focus and less activity in ipsilateral motor regions while performing a motor task.

FMRI was used to examine active brain regions in participants with FLE compared to controls while performing two motor tasks; the first, a finger-tapping task and the second, a more complex coordination task. Participant performance was scored to identify any functional motor deficits during task completion.

1.12.2 Specific Hypothesis 2

Motor regions ipsilateral to the seizure focus will display decreased resting-state connectivity to the contralateral motor cortex.

FMRI was used to identify differences in resting-state motor networks between participants with FLE and healthy controls.

Chapter Two: **Examination of Motor Regions Using Task-Based fMRI**

2.1 Introduction

Patients with FLE commonly experience motor deficits that negatively impact their day-to-day functioning. Motor impairments in FLE have been demonstrated in neuropsychological testing of motor control, coordination, and dexterity.[3] In addition, patients with FLE perform significantly worse compared to those with TLE when evaluated on tasks measuring psychomotor speed, attention, coordination, and sequencing.[7] These findings suggest that FLE may be associated with changes in the organization and communication of motor regions in the brain, similar to alterations in cortical language organization observed in TLE.[5] However, few studies have investigated functional motor changes in patients with seizure foci both within and distant from the motor cortex. A transcranial magnetic stimulation study of patients with FLE reported increased muscle representations in the unaffected hemisphere, and decreased representations of the same muscle in the affected hemisphere.[57] In addition, PET was used in patients undergoing early hemispherectomy to show that while motor function is generally reallocated to the contralesional hemisphere, it is not transferred to the primary motor region but to other adjacent cortices.[59] One limitation of these studies was poor spatial resolution compared to other currently available imaging techniques, namely fMRI.

FMRI provides high spatial resolution, can be task-based, and is non-invasive with no known risks. Individual FLE case studies show changes in motor representation in the brain using fMRI.[78,79] Most commonly, patients had increased activation in motor regions contralateral to the seizure focus regardless of which hand was performing the task. However, no fMRI studies to date have examined motor changes associated with FLE in general. One main reason

such studies are lacking is that changes in motor organization can be dependent on individual seizure focus location, seizure frequency, age at diagnosis, and types of seizures.[52,59]

FMRI can be used to assess organization of cortical motor areas using simple finger-tapping and more complex coordination tasks. Tapping tasks are advantageous due to their simplicity and ease of use for both healthy participants and those with motor impairments. Finger-tapping, however, does not elicit a brain response much beyond the most primary of motor regions.[80] More complex tasks, such as those requiring hand coordination, strongly elicit activity in secondary and tertiary motor regions not generally recruited during simple tapping tasks.[80] This type of recruitment pattern is more representative of that during typical daily functions. Unfortunately, the increased complexity excludes individuals with severe motor impairments from participating.

Currently, the source of functional motor deficits in patients with FLE is unknown. A task-based fMRI study was conducted to examine motor activation in individuals with FLE and it was hypothesized that recurrent seizure activity in the frontal lobe is associated with changes in motor organization within the brain. Specifically, participants with FLE were expected to exhibit greater activity in motor regions contralateral to the seizure focus and less activity in motor regions ipsilateral to the seizure focus, and that these changes would be exacerbated in individuals with increased seizure burden factors. Findings from this study may lead to a better understanding of the mechanisms underlying functional motor deficits in patients with FLE and could ultimately lead to better treatment and recovery options.

2.2 Methods

2.2.1 Participants

This study was approved by the ethics review board of the institution. Written informed consent was obtained from all participants prior to participation in the study.

Participants with FLE were identified through the Calgary Health Region Epilepsy Clinic, the Seizure Monitoring Unit at the Foothills Medical Center, and the Comprehensive Epilepsy Program, in Calgary, AB. Potential participants were between 16 and 65 years of age, right handed, and had a diagnosis of FLE confirmed by history, examination, routine EEG, video-EEG monitoring (VEM) and/or anatomical MR imaging. Participants were excluded from the study if they had a contraindication to MR imaging [including pregnancy, severe claustrophobia, metallic foreign bodies in the eye, and certain implanted medical devices (e.g., cardiac pacemaker, aneurysm clip)] as well as if they had previous brain surgery to manage epileptic seizures.

Ten non-epileptic controls were recruited through word of mouth and included relatives, colleagues, friends, and acquaintances. In order to participate in the study, controls had to be between the ages of 16 and 65, right handed, have no known neurological or psychiatric disorders, and no contraindications to MR imaging.

2.2.2 Simple and Complex Motor Tasks

Participants performed motor tasks by following a visual cue while in the scanner. A video projector (Avotec, Inc., Stuart, FL) situated behind the scanner projected visual stimuli onto a screen, which participants viewed using a mirror mounted on top of the head coil. Stimuli were created and presented using *Presentation* (Neurobehavioural Systems, Albany, CA).

Participants performed two motor tasks similar to Luria's Motor Sequences.[81] The first task required participants to tap their fingers in time with a visual cue (contrasting colours alternating at a 1s interval) (Figure 2.1). Each run consisted of alternating blocks of task (12s) and rest (24s) periods for a total of 3min and 48s (228s). The task was performed in separate runs with each hand unimanually, and synchronous bimanual tapping.

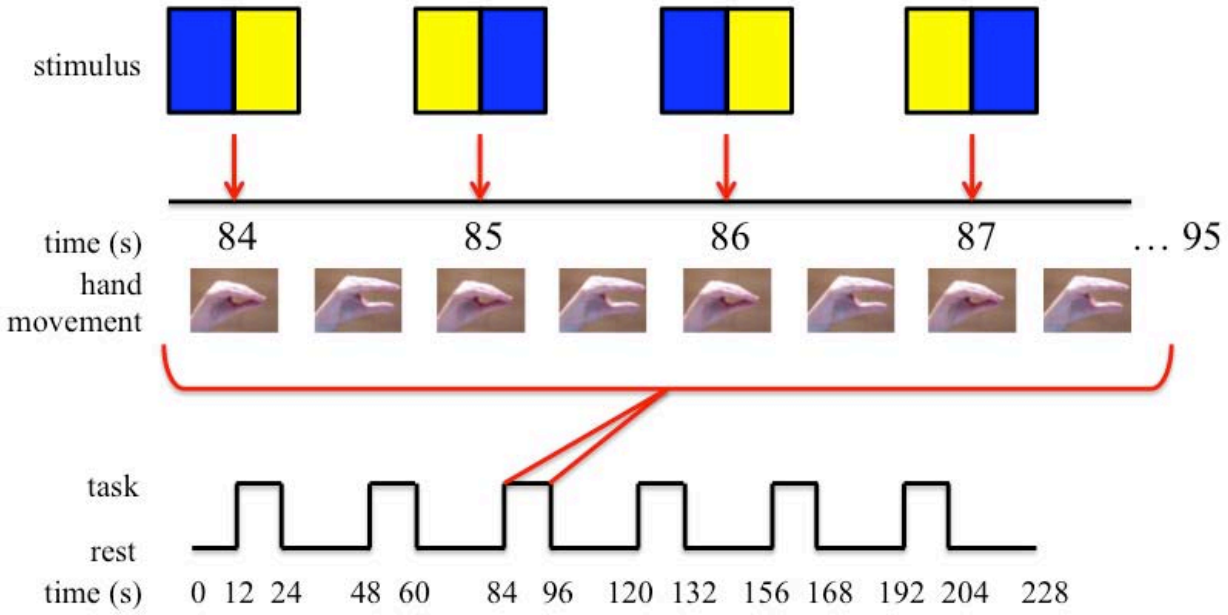


Figure 2.1 Timing and corresponding stimuli for the finger-tapping task. Bottom row indicates the timing of the 'on' (task)/'off' (rest) periods for an entire run. Images above demonstrate an example of the 'on' period. Stimulus presented to participants is shown in top row. Corresponding hand movements are shown below.

The second task was a motor coordination task, which required participants to perform a series of hand movements (circle = hand held in fist, vertical line = hand held vertically, horizontal line = hand held horizontally) paced at 2s intervals (Figure 2.2). Each run consisted of alternating blocks of task (24s) and rest (24s) for a total of 5min (300s), and was performed both

unimanually and bimanually in separate runs. During the bimanual coordination task, participants performed different hand movements with each hand simultaneously. A video camera was situated in the control room during the coordination tasks to record hand movements for later analysis. Participants' performance was rated blindly using a 4-point scale used by other groups (Table 2.1).[7]

During rest periods for both tasks, participants were instructed to focus on a central fixation cross. Participants were given the opportunity to practice the tasks outside of the scanner until they were comfortable performing them.

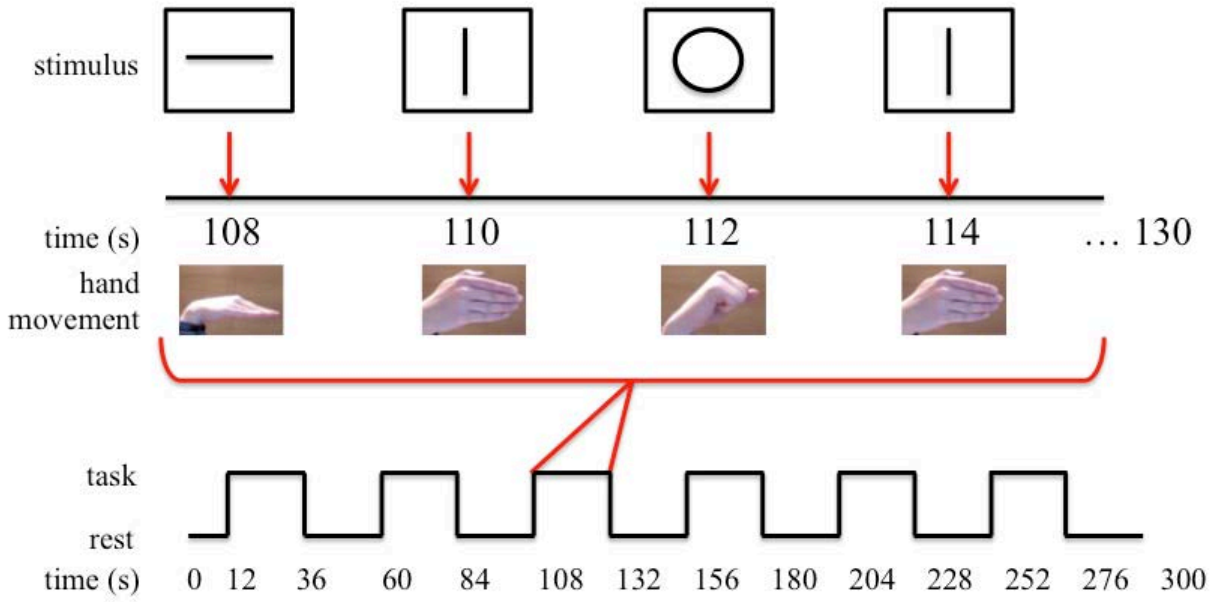


Figure 2.2 Timing and corresponding stimuli for the coordination task. Bottom row indicates the timing of the 'on' (task)/'off' (rest) periods for an entire run. Images above demonstrate an example of the 'on' period. Stimulus presented to participants is shown in top row. Corresponding hand movements are shown below.

Table 2.1 Performance scale used to rate each participant's hand movements during the coordination tasks.

Score	Description
1 (no impairment)	Participant performs the sequences correctly and fluently
2 (mild impairment)	Participant performs the sequences too slowly and/or with interruptions
3 (impairment)	Participant displays significant interference or inadequate strength while performing the sequences; movements cannot be separated and appear to be mixed, both hands perform same hand movement during bimanual task
4 (severe impairment)	Participant is unable to execute either the unimanual or bimanual sequence, or coordination breaks down after a few repetitions

2.2.3 FMRI Data Acquisition

Functional MR data were acquired using a 3.0 T GE Discovery MR750 whole body scanner (GE Healthcare, Waukesha, WI) with a receive-only 8-channel phased-array head coil (8 Channel High Resolution Brain Array, distributed by GE Medical Systems). MR images providing BOLD contrast were collected using a gradient-recalled echo, echo planar imaging (GRE-EPI) sequence (voxel dimensions 3.75 x 3.74 x 4 mm, 28 slices, 4-mm slice thickness, 64 x 64 matrix, TE = 30ms, TR = 1.5s, flip angle = 65 degrees). In total, six functional MR scans were completed: one for each finger-tapping task (left, right, bimanual) and one for each coordination task (left, right, bimanual). Participants also underwent a T_1-weighted multi-slice spoiled gradient echo sequence (28 x 4-mm slices, 128 x 128 matrix, minimum TE, TR = 150ms, flip angle = 18 degrees) and 3D magnetization-prepared gradient-echo sequence (2-mm slices, 384 x 256 x 112 matrix, preparation time = 500ms, minimum TE, TR = 8.9 ms, flip angle = 20 degrees) for anatomical registration of the fMRI data. Three-plane localizer images were performed for slice prescription

purposes and a higher-order shim sequence was applied immediately before the EPI sequence to minimize local magnetic field inhomogeneities.

Participants were asked to keep as still as possible while in the scanner. Each participant's head was immobilized using foam cushioning and participants had the option to terminate the study at any time during the scan using a squeeze ball placed by their side.

2.2.4 Data Analysis

2.2.4.1 Coordination Performance Scores

A Mann-Whitney-U test was conducted to determine if significant differences in the 4-point performance score existed between participants with FLE and controls. Also, a Kruskal-Wallis test was used to determine if performance score differed between right FLE, left FLE, and controls. Individual Mann-Whitney-U tests were then conducted between all group pairs, and a Bonferroni correction was applied to correct for multiple comparisons.

Participants with FLE were pooled and placed into one of two groups: non-impaired (participants with a score of 1) or impaired (participants with scores of 2,3 or 4). A MANOVA (multivariate analysis of variance) test was conducted to determine whether a significant difference existed in seizure demographics between the impaired and non-impaired group. Seizure demographics included age at epilepsy diagnosis, years since onset, seizures in lifetime (total/GTC seizures), seizures in past year (total/GTC seizures) and months since last seizure.

All analyses were conducted using IBM SPSS (Statistical Product and Service Solutions) Statistics Version 21 (IBM Corp, released 2012, Armonk, NY).

2.2.4.2 Pre-Processing of fMRI data

Pre-processing of image data was completed using FSL (fMRIB Software Library; http://www.fmrib.ox.ac.uk/fsl/)[82] to correct for non-physiological variability in the data. These steps included:

i) Brain extraction: Skull and scalp removal was performed using BET (Brain Extraction Tool) to improve anatomical registration of the fMRI data to the higher-resolution structural images.[83]

ii) Slice timing correction: Slices were collected in an interleaved pattern to avoid cross slice excitation. To correct for this, the MR signal time-course for each voxel was interpolated to the center of the imaging TR using Fourier-space time-series phase-shifting.

iii) Motion correction: Motion correction was performed using MCFLIRT (Motion Correction: FMRIB's Linear Image Registration Tool),[84] which uses a rigid-body transformation in order to minimize the effects of head movement on the data.

iii) Spatial smoothing: Spatial smoothing was performed in order to increase the signal-to-noise ratio by removing sharp high frequencies in the data and maintaining low frequencies. A 6mm FWHM (full width at half maximum) Gaussian kernel was used.

iv) Temporal filtering: A high-pass temporal filter was applied to the data in order to remove low frequency fluctuations that occur due to signal drift of a non-physiological origin (e.g., gradually changing magnetic field). A Gaussian-weighted least-squares straight line fitting with sigma = 100.0s was used.

v) Normalization: Grand-mean intensity normalization of the entire 4D dataset was conducting using a single multiplicative factor, indicating that each volume was scaled by the same amount.

2.2.4.3 First-Level Analysis

Once the data had been pre-processed, individual participant analyses were conducted using FEAT (fMRI Expert Analysis Tool, Version 5.90).[82] To begin, a model (e.g., task-based block design) was created that represented the expected time-course of a voxel's signal if it were active during task performance. For this study, one of two block designs was utilized: a period of alternating 24s OFF, 12s ON blocks for the finger-tapping task (Figure 2.1), and a period of alternating 24s ON, 24s OFF blocks for the coordination task (Figure 2.2). Block designs were convolved with the canonical hemodynamic response function in order to represent a voxels expected BOLD signal if its underlying neuronal activity correlated with the model (Figure 2.3).

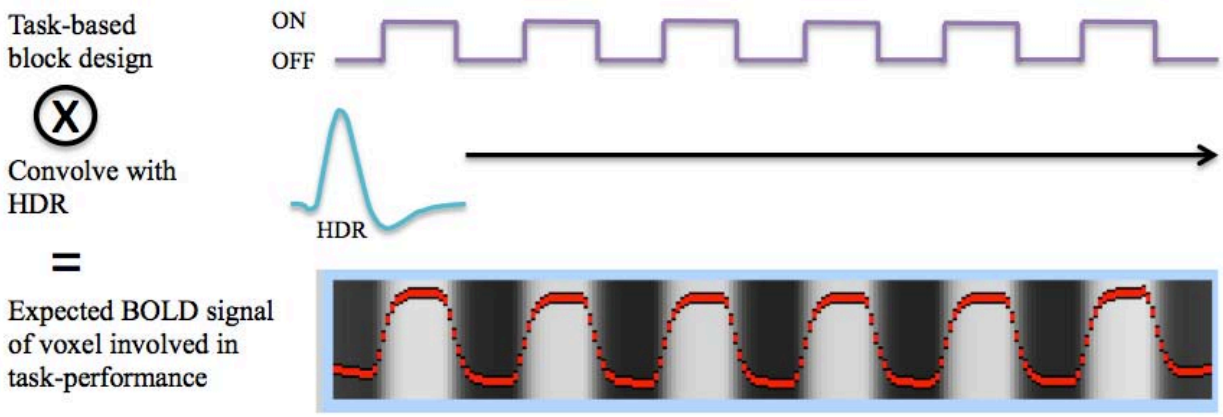


Figure 2.3 Expected time-course (model) that was compared with every voxel's BOLD signal time-course**.**

In order to compute the association between a voxel's actual BOLD signal time-course and the expected time-course, the general linear model was applied (generalization of multiple linear regression):

$$y(t) = X(t)*\beta + \varepsilon$$

where y(t) was the *observed* BOLD signal time-course from one voxel, X(t) was the *expected* time-course if the voxel was involved in the task, and β was a parameter estimate that was optimized in order to minimize ε, the residual error or noise that remained once the data had achieved best fit (i.e., parameter estimate had been optimized).

2.2.4.4 Higher-Level Analysis

Group analyses of parameter estimates were conducted to obtain mean activation maps for each task in each group. This analysis was carried out in FSL using FEAT, which utilizes the General Linear Mixed Model for higher-level analyses.[82] This process registered each first-level analysis' parameter estimates to the MNI152 standard brain (Copyright © 1993–2009 Louis Collins, McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University) in order to compute the average response magnitude for each voxel. Specifically, FSL's FLAME (FMRIB's Local Analysis of Mixed Effects) was used, which takes the session and participant variability into account, therefore allowing inferences to be made about the wider population and not only about individuals whom participated in the study.[82]

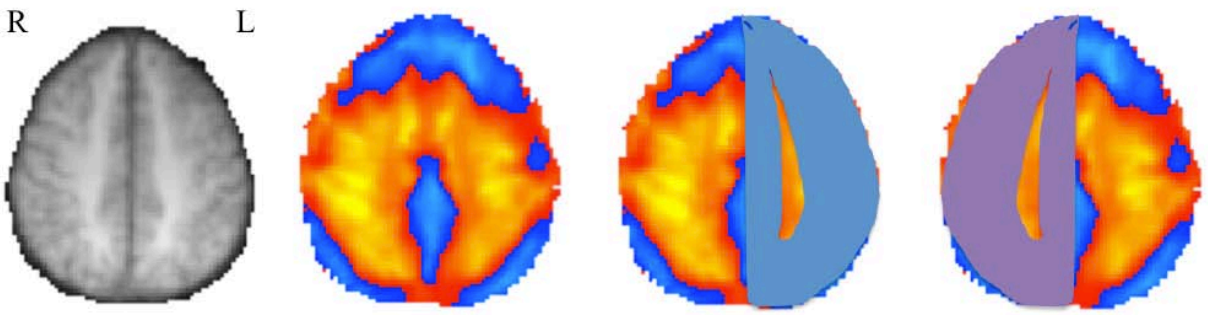
Contrasts of parameter estimates were generated to compute mean activation for each group and between groups and tasks. Specifically, the General Linear Mixed Model was applied by FSL to determine voxels exhibiting a significant difference in response magnitude between

groups and tasks. Participant's coordination performance scores were demeaned and entered as a covariate when computing both the mean and contrast images involving the coordination data.

Maps were generated using a Z-score>2.3 and a corrected cluster significance of p=0.05, as determined using AlphaSim,[85] a program that corrects for family wise error rates.

2.2.4.5 Relationship Between Laterality Indices and Seizure Demographic Factors

For each task laterality indices (LI) were calculated for each participant with FLE as well as for controls. LI is a way of measuring brain hemisphere dominance (greater activation) during performance of a task. First, a mask encompassing all cortical regions was created in standard space using the Harvard-Oxford cortical atlas.[86] This was done separately for both the left and right hemisphere. Whole-hemisphere masks were used because organizational changes occur in different cortical regions depending on the individual, not only in primary motor and secondary motor regions.[59] Masks were registered to each individual's native fMRI data space using FSL's FLIRT (FMRIB's Linear Image Registration Tool),[84] and Z-scores were determined for every voxel in the mask during the appropriate task. The total number of voxels as well as average Z-score was computed for both left and right hemisphere masks; LI was calculated using the resultant four values (Figure 2.4). A positive LI indicated left hemisphere dominance, a negative LI indicated right hemisphere dominance, and an LI of zero indicated the absence of any hemisphere dominance.



1. Individual data

2. Overlay task-based data from first-level analysis

3. Calculate number of voxels and average Z-score in left mask

4. Calculate number of voxels and average Z-score in right mask

$$LI = \frac{(\#\text{ voxels L})(\text{Z-score L}) - (\#\text{ voxels R})(\text{Z-score R})}{(\#\text{ voxels L})(\text{Z-score L}) + (\#\text{ voxels R})(\text{Z-score R})}$$

5. Calculate laterality index

Figure 2.4 Example of laterality index calculation using whole-hemisphere cortical masks.

For each of the right FLE and left FLE groups, LI was correlated to a number of seizure demographic factors. Factors included age at epilepsy diagnosis, years since diagnosis, lifetime seizures (total/GTC seizures), seizures in past year (total/GTC seizures), and number of months since last seizure. Spearman's rank correlation coefficients were determined for each relationship. Significant relationships were further explored by entering the seizure demographic factor as an explanatory variable in a revisited mean group analysis (FEAT) of each task.

2.3 Results

2.3.1 Participants

In total, 23 participants with FLE were recruited. One participant was excluded due to the inability to complete the entire study, two participants were later identified as left handed, and three participants had a change in their seizure diagnosis. This resulted in 17 participants; 11 right FLE and 6 left FLE (Table 2.2). Seizure foci were identified in one of seven frontal lobe regions: primary motor, supplementary sensorimotor, dorsolateral, orbitofrontal, anterior frontal, opercular, or cingulate. 10 control participants were recruited with a mean age of 33.9 $\pm$ 12.7 (range: 19-53) and included 5 males and 5 females.

2.3.2 Coordination Performance Scores

Coordination performance scores are listed in Table 2.3, and group comparisons are listed in Table 2.4. There was a significant difference between participants with FLE and controls ($p=0.011$), and participants with left FLE and controls ($p=0.024$). Seizure demographics were not significantly different between impaired and non-impaired participants ($p = 0.231$).

Table 2.2 Demographics of participants with FLE. Bottom row lists mean ± standard deviation for each column above. Seizure types are listed as GTC (generalized), CP (focal with dyscognitive features), or SP (focal without dyscognitive features). Seizure burden was evaluated at the time of study as low (seizures every 6 months or longer), moderate (every 1-6 months), high (every 2-4 weeks), or very high (every 2 weeks or less).

Gender	Age at scan	Age at epilepsy onset	Seizure burden	Months since last seizure	Seizure focus	Seizure types
Participants with Right FLE						
M	16	7	Low	7	Supplementary sensorimotor	GTC, CP
F	20	12	Moderate	0	Primary motor	GTC, CP, SP
F	21	18	Moderate	2	Anterior frontopolar	GTC
M	24	4	Moderate	8	Primary motor	SP
M	25	17	Low	32	Anterior frontopolar	GTC
F	29	5	Very high	0	Opercular	CP
M	32	26	Moderate	14	Anterior frontopolar	SP
M	33	28	Low	20	Anterior frontopolar	CP
F	36	0	Low	10	Supplementary sensorimotor	GTC, CP
M	46	39	Low	13	Anterior frontopolar	GTC, CP
M	47	28	Low	112	Supplementary sensorimotor	GTC
7M/4F	**29.9 ± 10.2**	**16.7 ± 12.4**		**19.8**		
Participants with Left FLE						
M	19	4	Low	6	Supplementary sensorimotor	GTC, CP, SP
M	28	2	Very high	2	Primary motor	GTC, CP, SP
M	30	8	High	0	Primary motor	GTC, SP
M	39	2	Very high	1	Dorsolateral	GTC, CP
F	55	12	Low	18	Primary motor	GTC, SP
F	65	41	Low	30	Primary motor	CP, SP
4M/2F	**39.3 ± 17.5**	**11.5 ± 15.0**		**9.5**		

Table 2.3 Number of participants in each group receiving each coordination performance score.

Score	Controls (n=10)	Right FLE (n=11)	Left FLE (n=6)
1 (no impairment)	10	7	2
2 (mild impairment)	0	4	2
3 (impairment)	0	0	2
4 (severe impairment)	0	0	0
Average Score	1.0 $\pm$ 0.0	1.4 $\pm$ 0.5	2.0 $\pm$ 0.9

Table 2.4 Comparison of coordination performance scores between each of the three groups, analyzed using Kruskal-Wallis (KW) and Mann-Whitney-U (MW) tests. Significant differences ($p<0.05$) are shown in bold and marked by an asterisk (*).

Comparison	P-value	Bonferroni corrected p-value (when necessary)
FLE vs Controls (MW)	0.011 (1-tailed)	**0.011***
All three groups (KW)	0.012	**0.012***
Right FLE vs Controls (MW)	0.055 (1-tailed)	0.165
Left FLE vs Controls (MW)	0.008 (1-tailed)	**0.024***
Right FLE vs Left FLE (MW)	0.080 (2-tailed)	0.450

2.3.3 Group Averages

2.3.3.1 Similarities

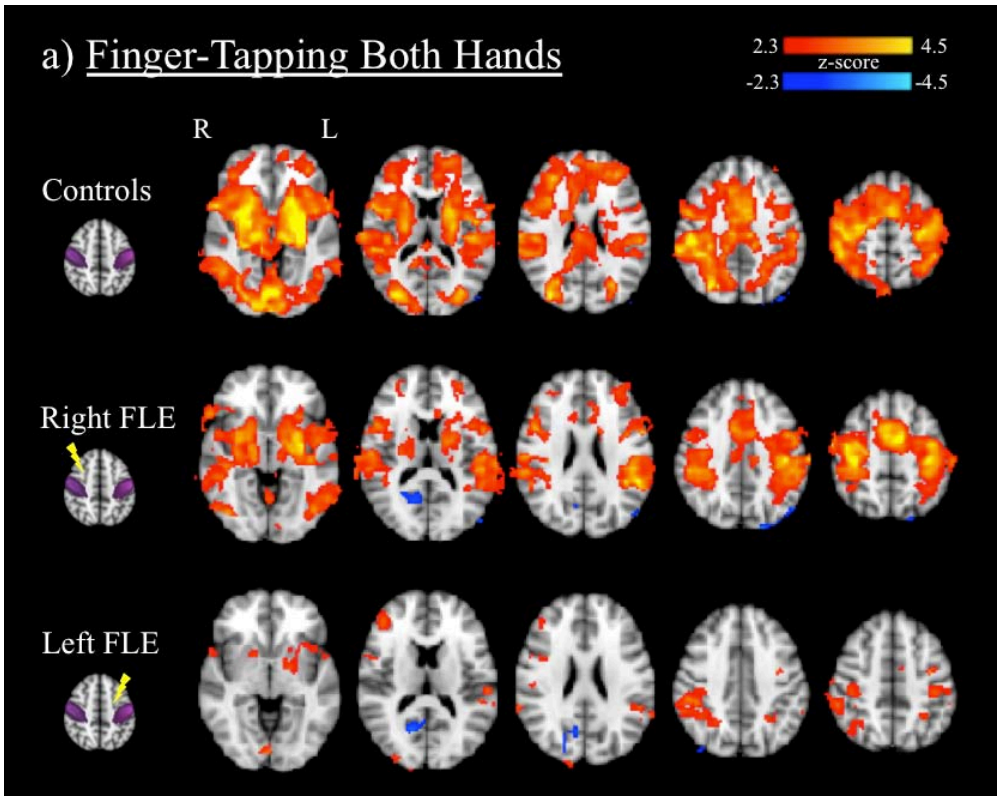
All three groups (control, right FLE, left FLE) demonstrated significant activation in similar brain regions during all six motor tasks (Figure 2.5 a-f). This included primary motor, premotor, supplementary motor, prefrontal, posterior parietal, and lateral occipital cortex**.** Active subcortical structures included the putamen, globus pallidus, thalamus, and caudate. Common areas showing decreased activity during task performance included the medial prefrontal cortex, posterior cingulate, angular gyrus, and posterior insula (all part of the default mode network).[87,88] The bimanual tasks (Figure 2.5 a,b) elicited expected bilateral activation of the primary motor cortex, superior parietal cortex, and premotor cortex. Activation of these regions was unilateral

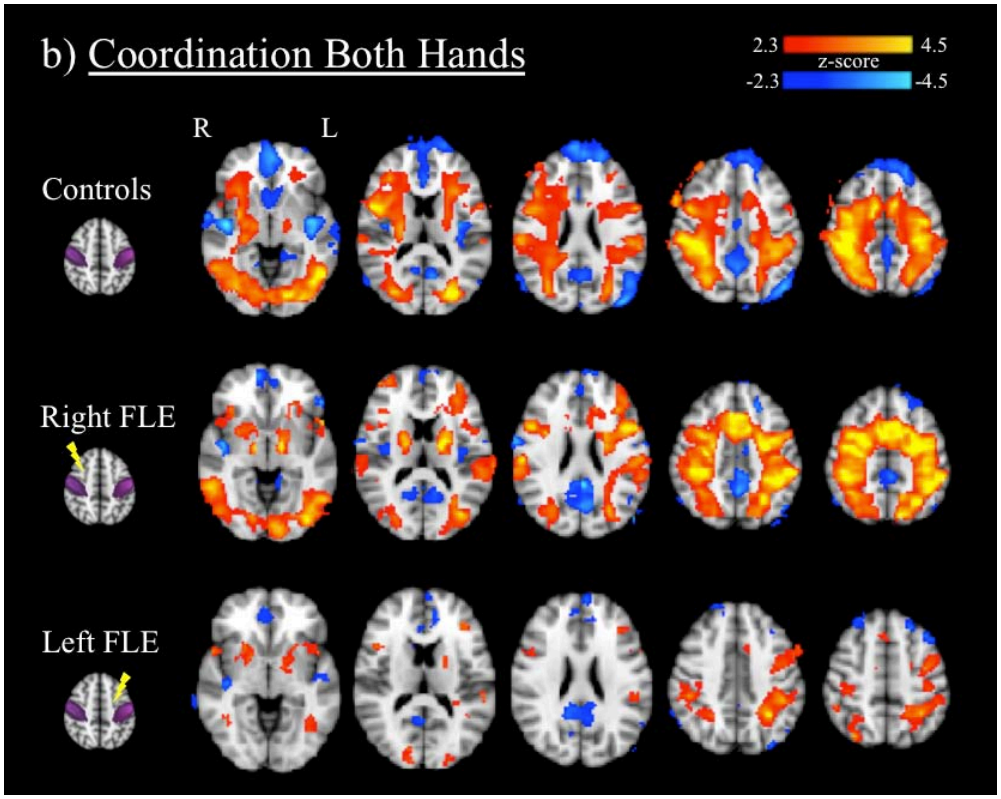
in unimaual tasks, being right hemisphere dominant in left handed tasks (Figure 2.5 c,d) and left hemisphere dominant in right handed tasks (Figure 2.5 e,f).

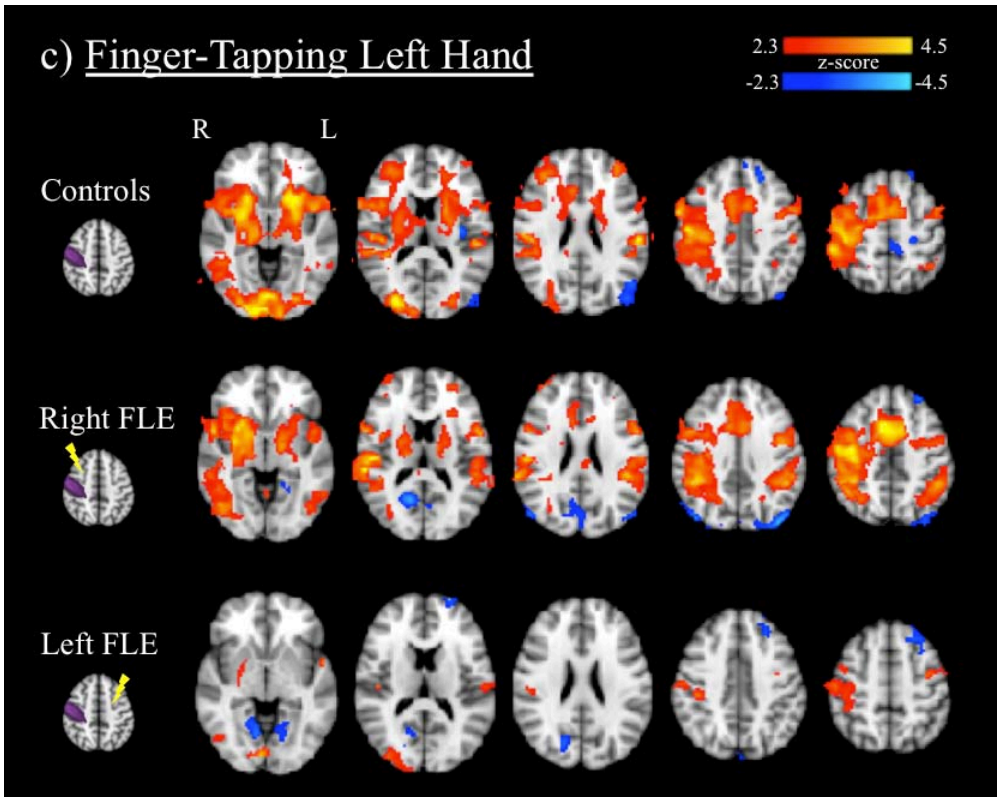
2.3.3.2 Differences

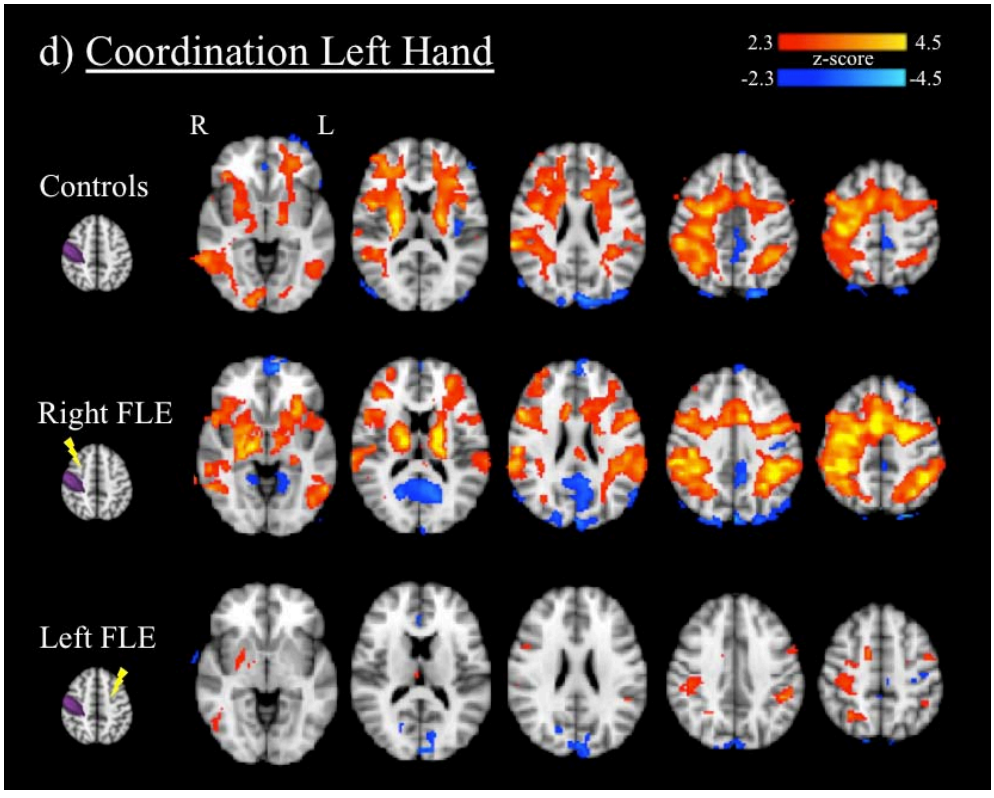
Left handed tasks revealed more bilateral activation in participants with right FLE compared to controls, whom primarily had right hemisphere activation (Figure 2.5 c,d). In fact, right FLE activation was similar during left handed and bimanual tasks.

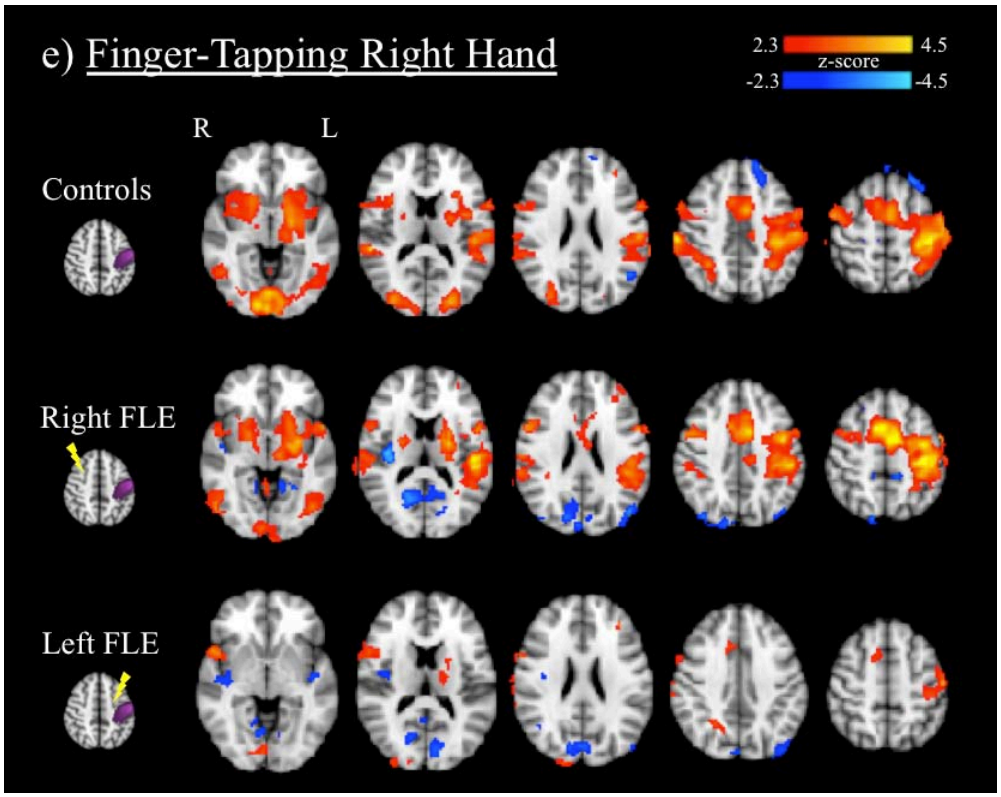
Participants with left FLE had smaller regions of activation and lower Z-scores. Bilateral motor activation occured in both bimanual tasks (Figure 2.5 a,b); however there was more activation in the right hemisphere during the bimanual finger-tapping task, specifically in the right superior parietal cortex.


a) Finger-Tapping Both Hands
2.3
4.5
z-score
-2.3
-4.5
R
L
Controls
Right FLE
Left FLE


b) Coordination Both Hands
2.3
4.5
z-score
-2.3
-4.5
R
L
Controls
Right FLE
Left FLE


c) Finger-Tapping Left Hand
2.3
4.5
z-score
-2.3
-4.5
R
L
Controls
Right FLE
Left FLE


d) Coordination Left Hand
2.3
4.5
z-score
-2.3
-4.5
R
L
Controls
Right FLE
Left FLE


e) Finger-Tapping Right Hand
2.3
4.5
z-score
-2.3
-4.5
R
L
Controls
Right FLE
Left FLE

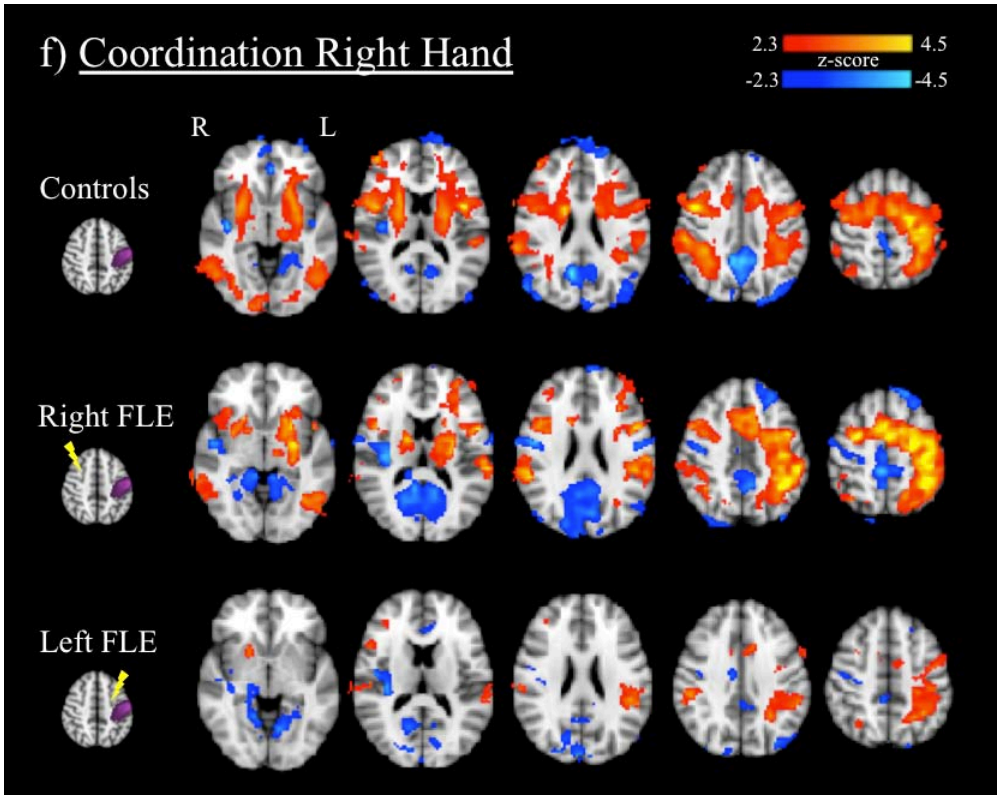

f) Coordination Right Hand
2.3
4.5
z-score
-2.3
-4.5
R
L
Controls
Right FLE
Left FLE

Figure 2.5 Group average fMRI data for a) bimanual finger-tapping task, b) bimanual coordination task, c) left handed finger-tapping task, d) left handed coordination task, e) right handed finger-tapping task, and f) right handed coordination task. Anatomical images in the inset on the left show the side of the seizure foci for the group (lightning bolt) and typical motor cortex recruitment for the task (purple shading).

2.3.4 Between and Within Group Contrast Images

2.3.4.1 Right FLE vs Controls

Figure 2.6 shows the statistical comparison between right FLE and controls during the finger-tapping and coordination tasks. Participants with right FLE had increased left (healthy) hemisphere activation, decreased right (epileptic) hemisphere activation, or a combination of both during task performance.

During finger-tapping tasks, participants with right FLE exhibited less activity in the right hemisphere compared to controls (Figure 2.6 a). In the bimanual finger-tapping task this occurred in cortical structures including the frontal pole, insula, posterior cingulate, paracingulate, occipital cortex, precuneus, and supramarginal gyrus, and subcortically in the right globus pallidus and thalamus. The unimanual tapping tasks showed less activity in the right occipital pole and supramarginal gyrus.

During coordination tasks, participants with right FLE had greater activation in the left hemisphere, and less activation in the right hemisphere (Figure 2.6 b). These participants showed greater activation in the superior and middle temporal gyrus, insular cortex, anterior cingulate, superior parietal cortex, and superior frontal gyrus during the bimanual coordination task, and less activation was seen in the insular cortex and precentral gyrus. During the left handed coordination task, participants with right FLE showed greater activity in the supramarginal gyrus and precentral/middle frontal gyrus. In the right handed coordination task they had decreased activity in the occipital pole, superior parietal cortex, and precentral gyrus.

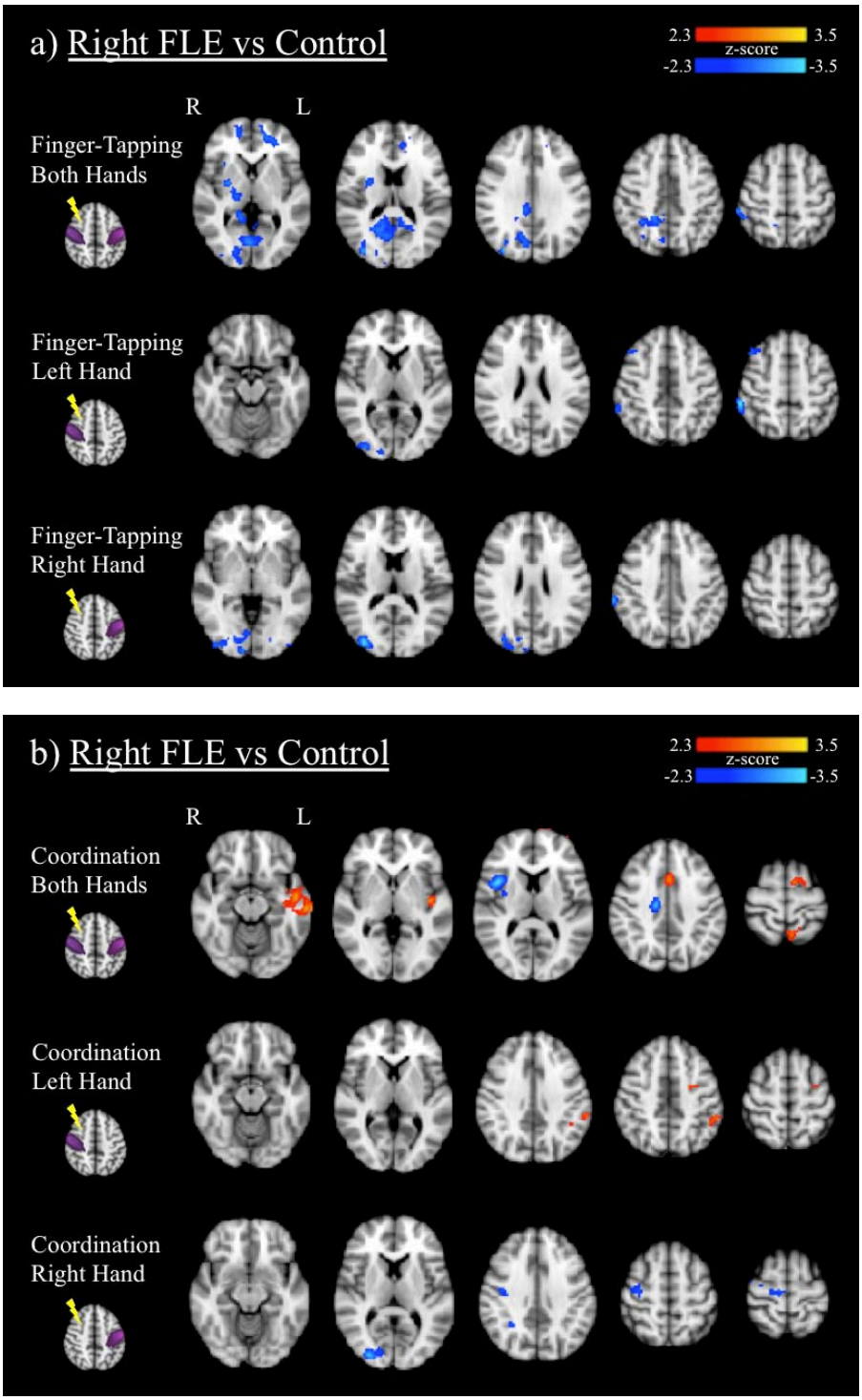


Figure 2.6 Comparison between participants with right FLE and controls during a) finger-tapping and b) coordination tasks. Areas of red indicate regions *more* active in participants with right FLE compared to controls during task performance, and areas of blue indicate regions *less* active in participants with right FLE compared to controls during task performance. Anatomical images in the inset on the left show the side of seizure foci for the group (lightning bolt) and typical motor cortex recruitment for the task (purple shading).

2.3.4.2 Left FLE vs Controls

Figure 2.7 shows the statistical comparison between left FLE and controls during the finger-tapping and coordination tasks. All finger-tapping tasks were associated with less activity in posterior cingulate in participants with left FLE (Figure 2.7 a). Participants with left FLE also showed less activity in the left frontal pole, precuneus, and cingulate during the bimanual finger-tapping task, and in the right putamen during the bimanual and left handed finger-tapping tasks.

Differences between participants with left FLE and controls during coordination tasks were observed primarily in the white matter and therefore likely due to artefact (Figure 2.7 b). In the bimanual coordination task, artefact was seen in white matter adjacent to the insula. The left handed coordination task was also associated with white matter artefact, along with less activity in the right supramarginal gyrus in participants with left FLE. Less activity during the right handed task was seen in the right putamen and thalamus.

2.3.4.3 Right FLE vs Left FLE

Figure 2.8 shows the statistical comparison between participants with right and left FLE during the finger-tapping and coordination tasks.

2.3.4.3.1 Increases in Participants with Right FLE

Increased activation was seen in the right putamen in participants with right FLE during bimanual finger-tapping and both left handed tasks, while the left putamen was more active during both right handed tasks (Figure 2.8). Increased frontal activation occurred in participants with right compared to left FLE in most tasks, however there was no clear pattern of lateralization. There was greater *right* frontal pole activity during bimanual finger-tapping and

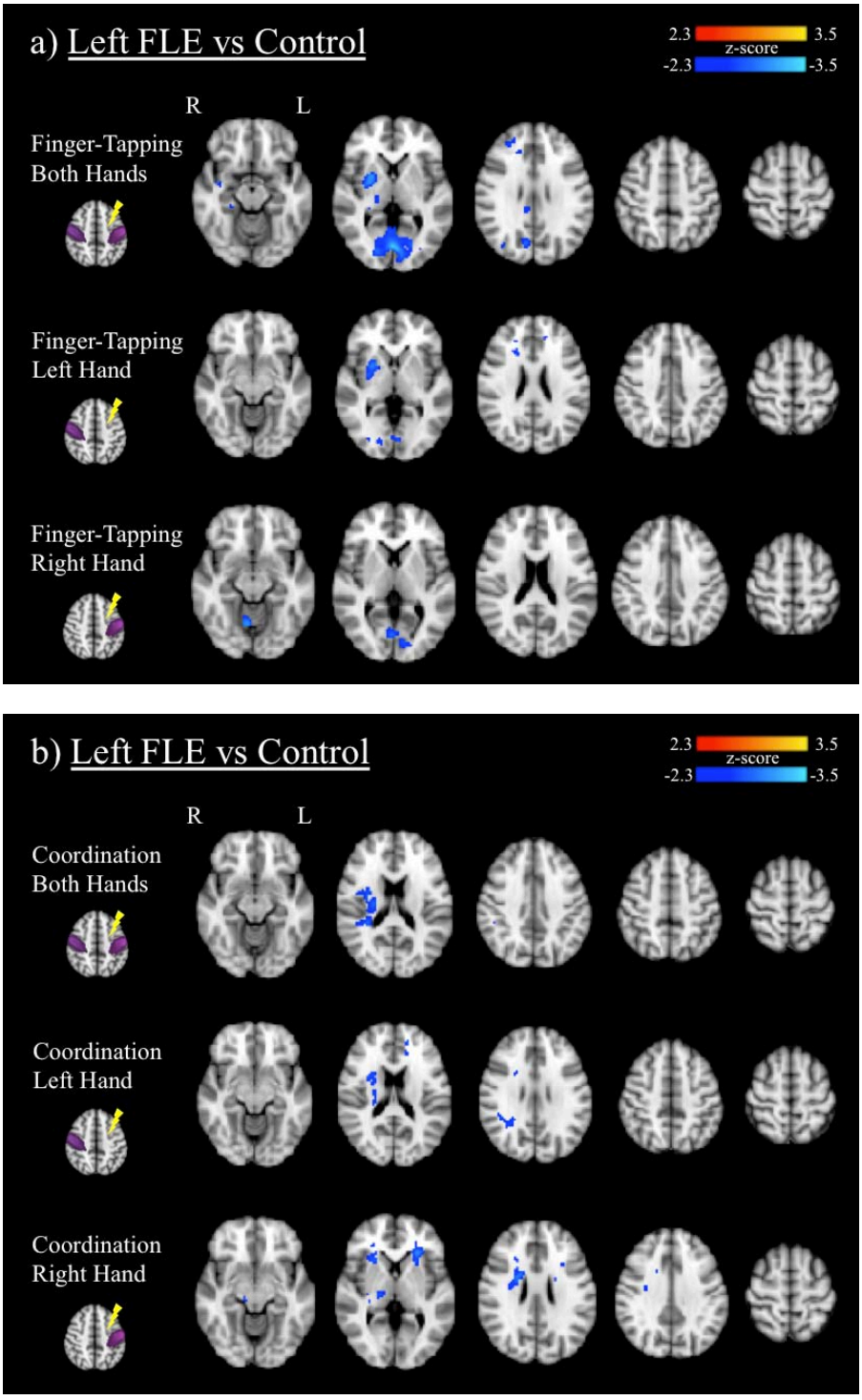


Figure 2.7 Comparison between participants with left FLE and controls during a) finger-tapping and b) coordination tasks. Areas of red indicate regions that were *more* active in participants with left FLE compared to controls during task performance, and areas of blue indicate regions that were *less* active in participants with left FLE compared to controls during task performance. Anatomical images in the inset on the left show the side of seizure foci for the group (lightning bolt) and typical motor cortex recruitment for the task (purple shading).

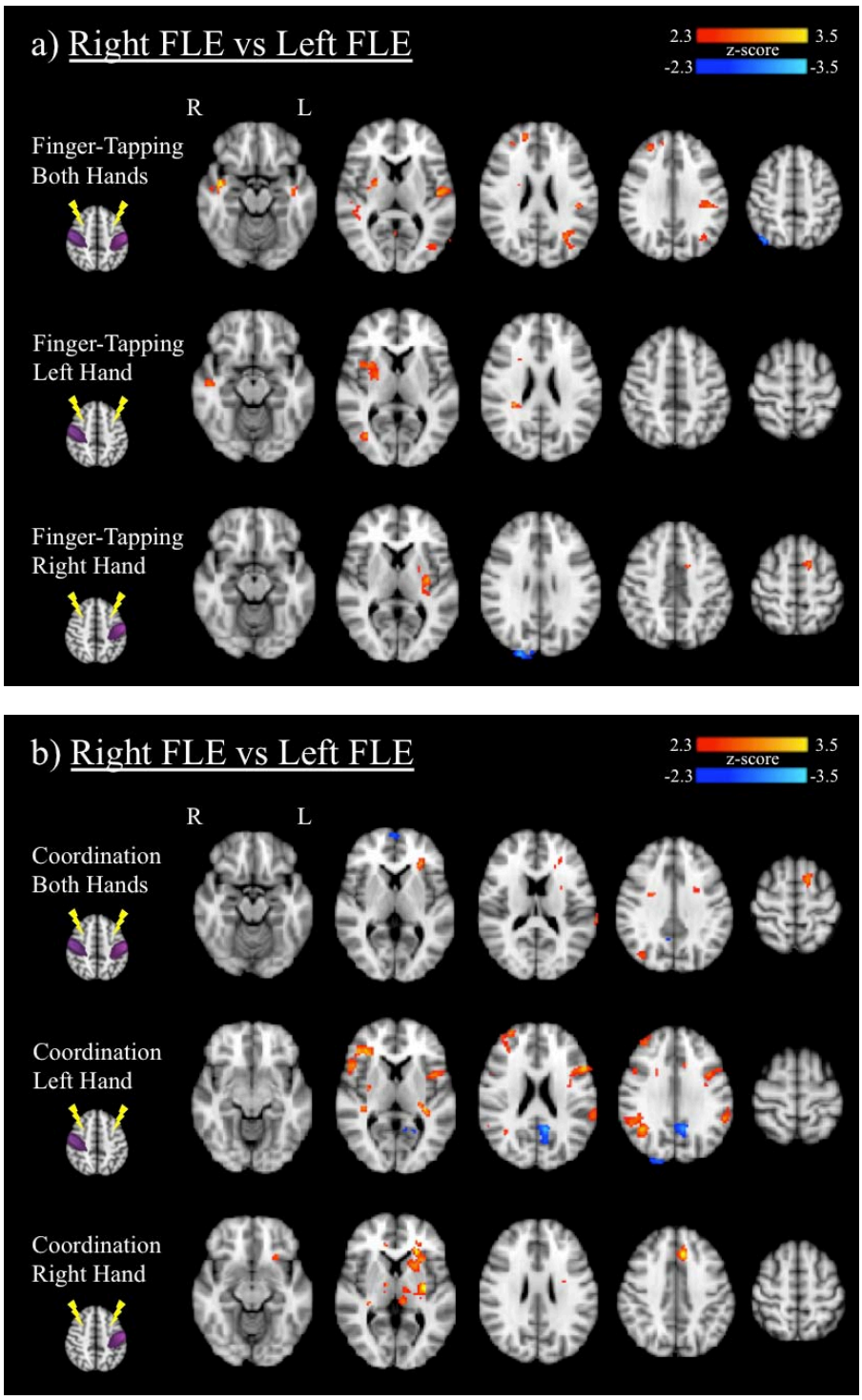


Figure 2.8 Comparison between participants with right and left FLE during a) finger-tapping and b) coordination tasks. Areas of red indicate regions *more* active in participants with *right compared to left FLE* during task performance, and areas of blue indicate regions *more* active in participants with *left compared to right FLE* during task performance. Anatomical images in the inset on the left show the side of seizure foci for the group (lightning bolt) and typical motor cortex recruitment for the task (purple shading).

left handed coordination, but greater *left* superior frontal gyrus activity during bimanual coordination and right handed finger-tapping tasks. The *left* opercular region in bimanual finger-tapping, and the *left* paracingulate region in right and left handed coordination tasks were also more active in participants with right FLE.

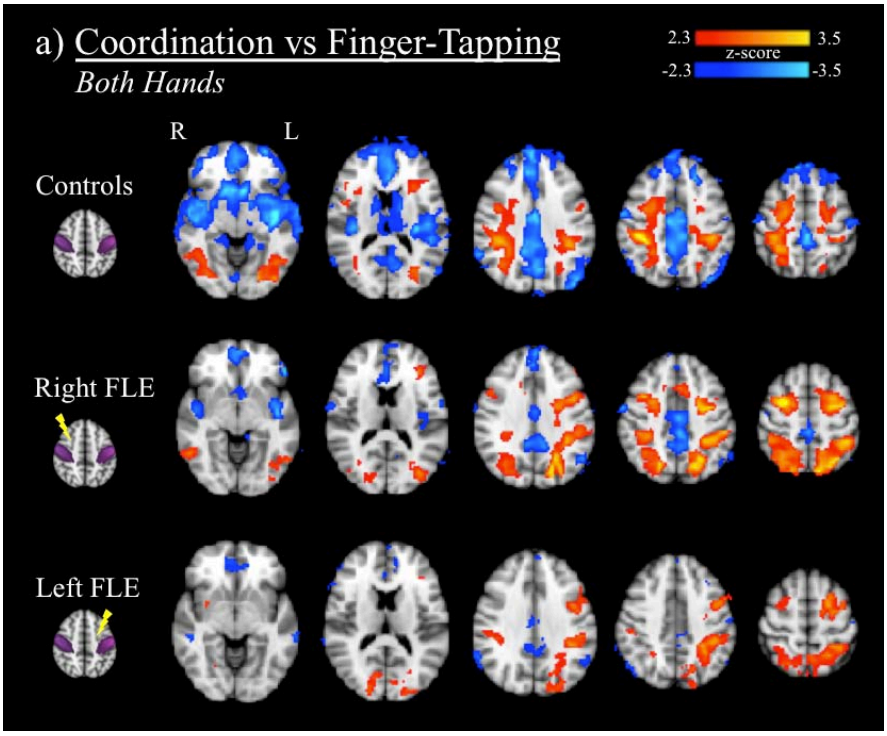
Additional regions of increased activity in participants with right compared to left FLE were primarily observed in the parietal cortex, specifically in the supramarginal and angular gyrus. This occurred bilaterally during the left handed coordination task and in the left hemisphere during the bimanual finger-tapping task.

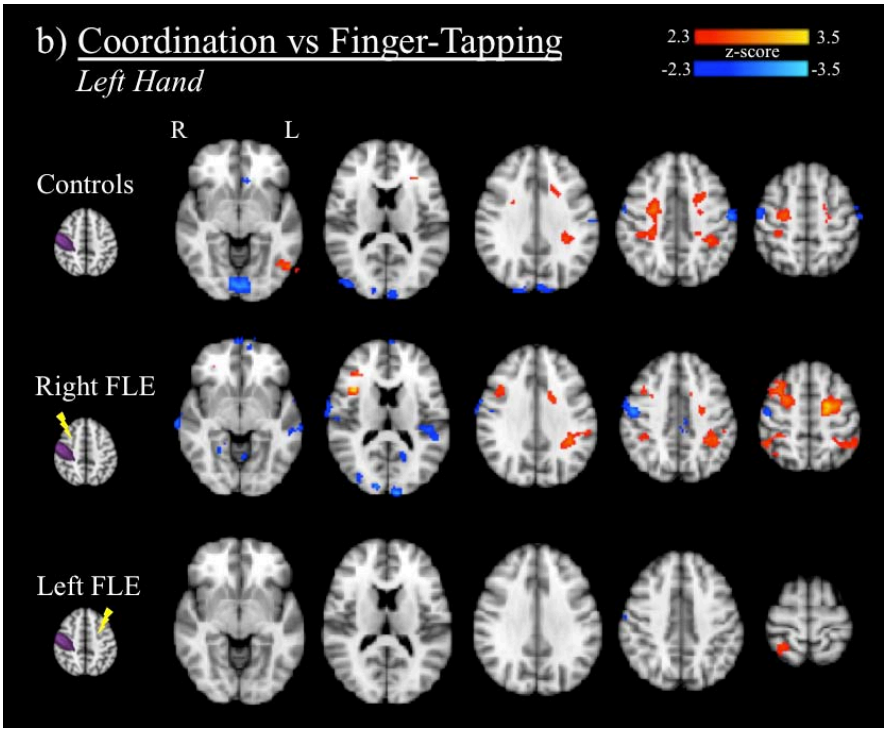
2.3.4.3.2 Increases in Participants with Left FLE

Participants with left FLE had increased activity in the right angular gyrus during bimanual finger-tapping, and right lateral occipital cortex during right handed finger-tapping (Figure 2.8 – this is shown in blue). They also had increases in the posterior cingulate during left handed coordination, and in the medial prefrontal cortex during bimanual coordination.

2.3.4.4 Coordination vs Finger-Tapping Tasks

Figure 2.9 shows the statistical comparison between the coordination and finger-tapping tasks in all three participants groups. Regions of increased activity during coordination tasks included the lateral occipital cortex**,** prefrontal cortex, and posterior parietal cortex (Figure 2.9). These regions were fairly consistent in all groups and were most prounouced during the bilateral tasks (Figure 2.9 a); however, they were more lateralized to the left hemisphere in participants with FLE. All comparisons also revealed greater default mode network suppression (less activity) during


a) Coordination vs Finger-Tapping
Both Hands
2.3
3.5
z-score
-2.3
-3.5
R
L
Controls
Right FLE
Left FLE


b) Coordination vs Finger-Tapping
Left Hand
2.3
3.5
z-score
-2.3
-3.5
R
L
Controls
Right FLE
Left FLE

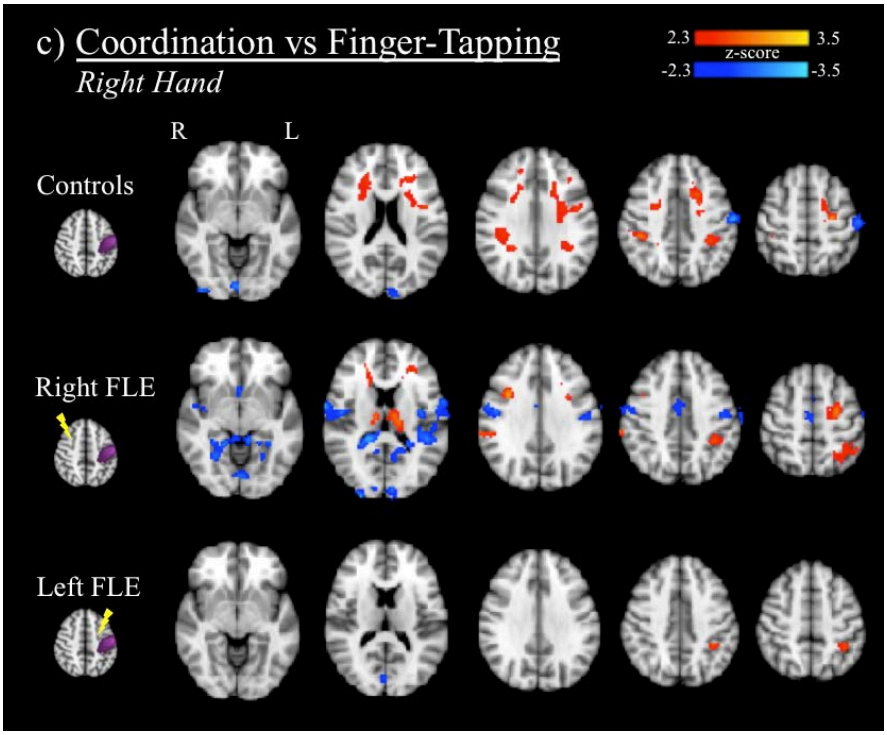


Figure 2.9 Comparison between coordination and finger-tapping tasks a) bimanually, b) unimanually with the left hand, and c) unimanually with the right hand. Areas of red indicate regions that were *more* active during the coordination compared to the finger-tapping task, and areas of blue indicate regions that were *less* active during the coordination task compared to the finger-tapping task. Anatomical images in the inset on the left show the side of seizure foci for the group (lightning bolt) and typical motor cortex recruitment for the task (purple shading).

coordination tasks. This included the posterior cingulate, medial prefrontal cortex, and inferior parietal cortex.

Controls had less activation in the *left* sensorimotor cortex during unimanual coordination tasks (Figure 2.9 b,c). Contrarily, participants with right FLE showed less *right* sensorimotor activity during left and right handed coordination tasks (Figure 2.9 b,c). No significant differences occured in sensoriotor cortex of participants with left FLE when comparing unimanual tasks.

2.3.5 Relationship Between LIs and Seizure Demographic Factors

LIs during coordination tasks were used instead of finger-tapping tasks because coordination tasks were associated with recruitment of additional motor regions (Figure 2.9). Control participants had LIs between -1 and +1 during the right and left handed coordination tasks.

2.3.5.1 Participants with Right FLE

A negative correlation between LI and the number of months since last seizure was observed for participants with right FLE during the left handed cooridination task (Figure 2.10, top). In addition, a positive correlation between LI and the number of GTC seizures in the previous year was seen for the same participants and the same task (Figure 2.11, top). Age at onset, years since diagnosis, number of lifetime seizures (total/GTC seizures) and total number of seizures in the past year were not correlated to LIs of the left handed coordination task. No significant relationship was seen between seizure demographics and LIs of the right handed coordination task.

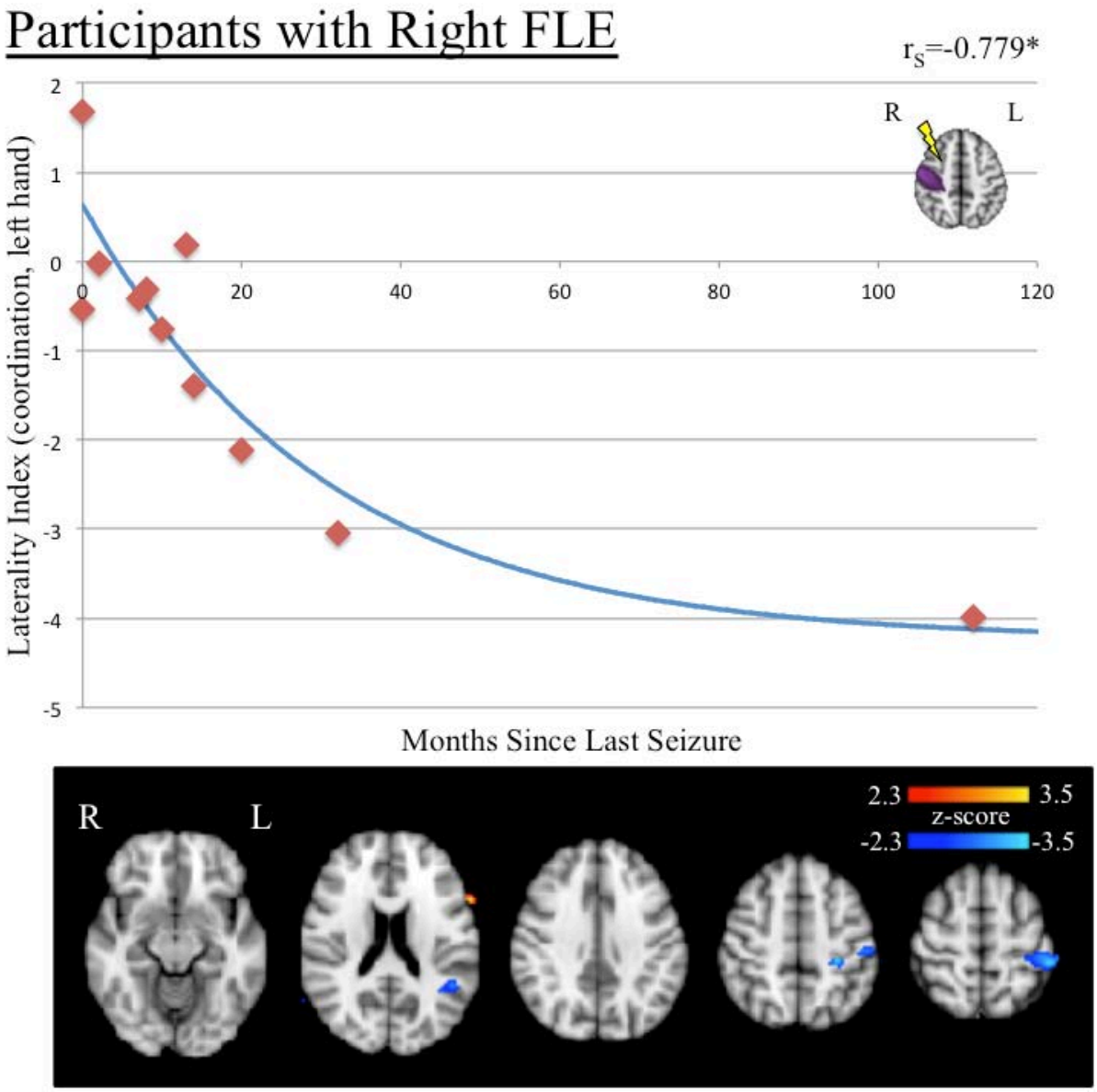


Figure 2.10 Top: Relationship between LI of the left handed coordination task and months since last seizure in participants with right FLE. Spearman's rank correlation coefficient is in the top right hand corner. Positive laterality index indicates left hemisphere dominance and negative laterality index indicates right hemisphere dominance. Bottom: Images showing brain regions that were more active (red) or less active (blue) during the left handed coordination task in participants with a *greater* number of months since last seizure. The anatomical image on the top right shows the side of seizure foci for the group (lightning bolt) and typical motor cortex recruitment for the task (purple shading).

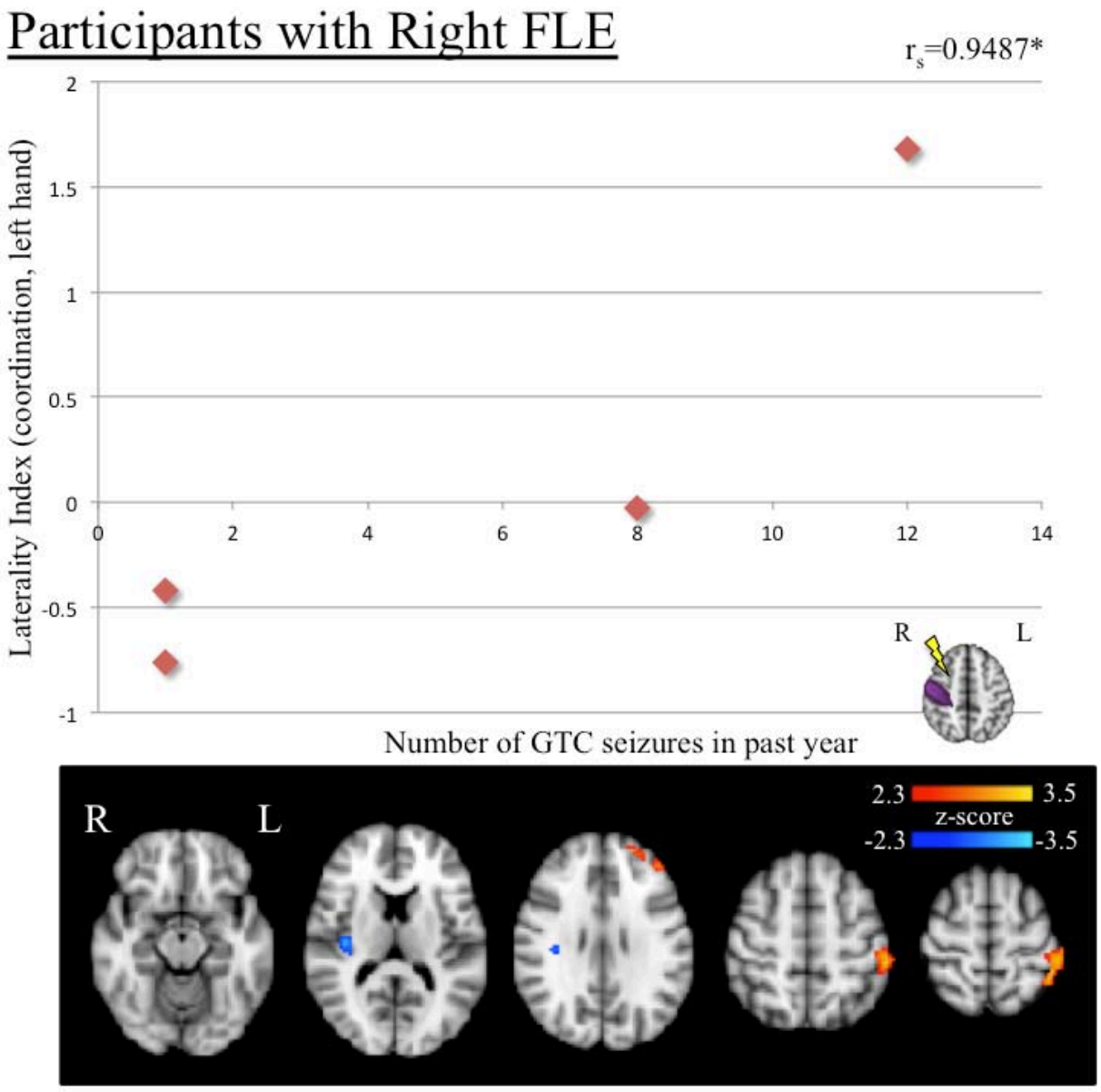


Figure 2.11 Top: Relationship between LI of left handed coordination task and number of GTC seizures in the past year in participnats with right FLE. Spearman's rank correlation coefficient is in the top right hand corner. Positive laterality index indicates left hemisphere dominance and negative laterality index indicates right hemisphere dominance. Bottom: Images showing brain regions that were more active (red) or less active (blue) during the left handed coordination task in participants with *more* GTC seizures in the past year. The anatomical image on the bottom right shows the side of seizure foci for the group (lightning bolt) and typical motor cortex recruitment for the task (purple shading).

Participants with right FLE with recent seizures showed greater left hemisphere dominance during left handed coordination, while those with longer seizure freedom had greater right hemisphere dominance (Figure 2.10, top). Five participants with right FLE fell either above or below the control ('normal') LI range (-1 to +1). Functional activation maps (Figure 2.10, bottom) showed that with longer periods of seizure freedom, participants with right FLE used their left sensorimotor cortex and supramarginal gyrus *less* during the task, hence making their LI more negative. Alternatively, individuals with recent seizures use these regions *more* to perform the task, hence making their LI more positive.

Participants with right FLE with more GTC seizures in the past year showed increased left hemisphere dominance during the left handed coordination task, compared to those who experienced fewer GTC seizures (Figure 2.11, top). Only participants with GTC seizures in the past year were included in analyses, resulting in very low numbers (n=4). Participants with more GTC seizures in the past year showed greater activity in the left sensorimotor cortex during the task compared to participants with fewer GTC seizures, as well as small increases in the left prefrontal cortex and decreases in the right insular cortex (Figure 2.11, bottom).

2.3.5.2 Participants with Left FLE

No significant correlations were seen between seizure demographics and LI of the left handed coordination task in participants with left FLE. LI for the right handed task was significantly correlated with number of months since last seizure (Figure 2.12, top). Specifically, participants with longer seizure freedom had greater left hemisphere dominance, while those with

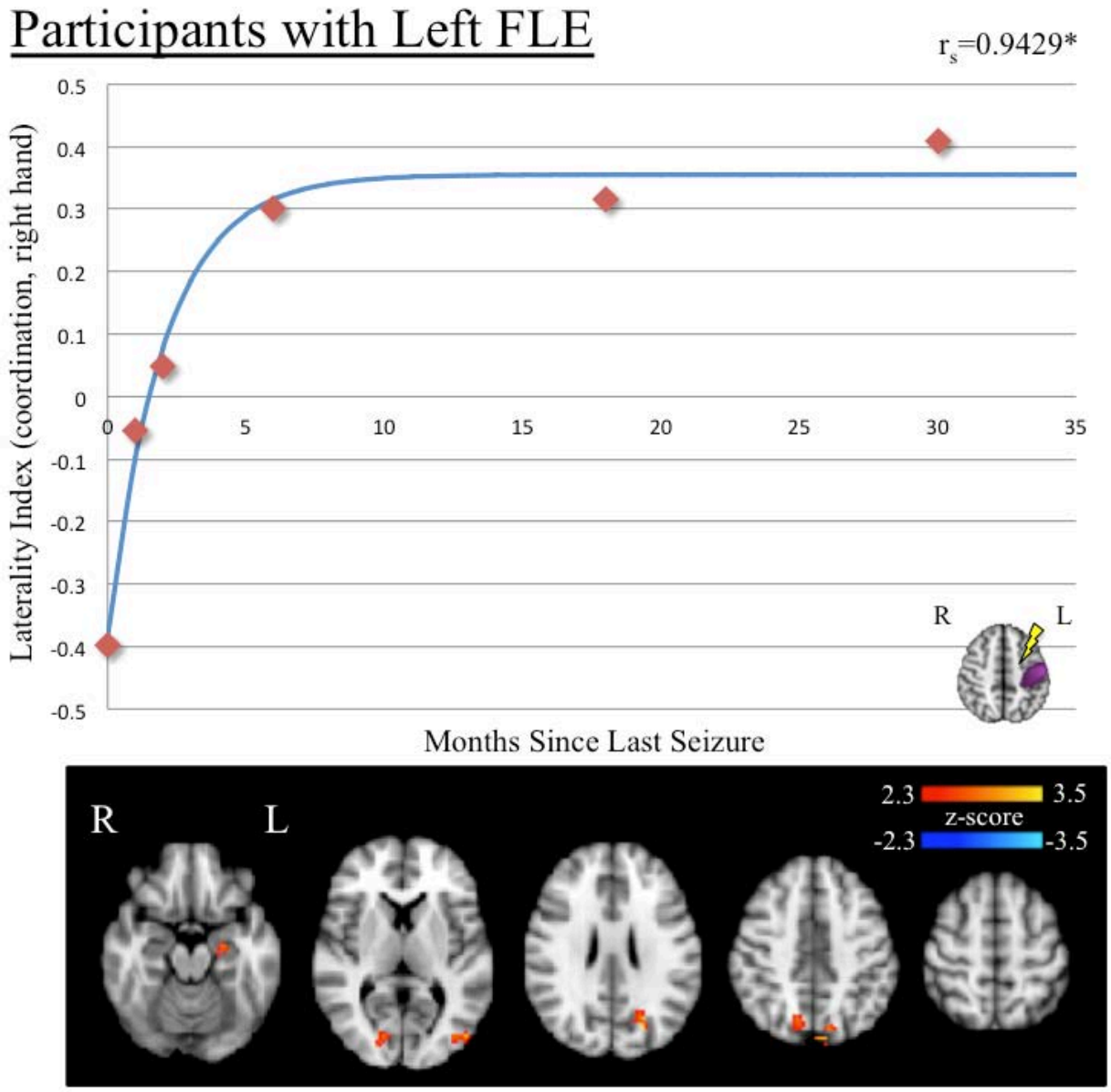


Figure 2.12 Top: Relationship between LI of the right handed coordination task and months since last seizure in participants with left FLE. Spearman's rank correlation coefficient is in the top right hand corner. Positive laterality index indicates left hemisphere dominance and negative laterality index indicates right hemisphere dominance. Bottom: Images showing brain regions that were more active (red) or less active (blue) during the left handed coordination task in participants with a *greater* number of months since last seizure. The anatomical image on the bottom right shows the side of seizure foci for the group (lightning bolt) and typical motor cortex recruitment for the task (purple shading).

recent seizures had greater right hemisphere dominance (Figure 2.12, top). Regions that demonstrated greater activity with longer seizure freedom included bilateral occipital and superior parietal cortex (Figure 2.12, bottom).

2.4 Discussion

2.4.1 Behavioural Findings

Participants with FLE performed significantly worse than controls during the coordination task (see Table 2.4). This has been demonstrated previously, both clinically in participants with FLE[3,7] and experimentally in rat models of epilepsy,[20] with results showing deficits in coordination, motor dexterity, motor programming, and psychomotor speed.

In the present study, only participants with *left* FLE performed significantly worse than controls. Experimental evidence is conflicting regarding the effects of FLE lateralization on behavioural measures. Some studies have reported no significant difference when measuring motor skills in patients with right and left FLE, and suggested that similarities were due to contralateral seizure propagation, triggering bilateral motor deficits.[2,7,19,89] However, differences have been detected in bimanual coordination tasks, with patients with left FLE performing significantly worse than those with right FLE.[19]

Differences between participants with right and left FLE could be due to dissimilar arrays of seizure foci and not because of seizure lateralization. Most studies were unable to distinguish lesion location within frontal lobe sub-regions based on neuropsychological testing, including tasks measuring speed, attention, motor sequencing, and coordination.[19,89] However, one study observed differences in bimanual coordination performance; patients with motor/premotor FLE performed worse than those with un-localized and dorsolateral FLE.[19]

Separating participants with FLE into non-impaired and impaired groups disclosed no significant differences between seizure demographics; however, this could be due to a limited number of participants. Previous studies have demonstrated deficits on neuropsychological tests in relation to seizure demographics; greater seizure frequency and increased secondary generalized seizures affected IQ scores, specifically on measurements of psychomotor speed, sequencing, and cognitive flexibility.[19,89] Studies have also demonstrated significantly poorer performance on these measures in patients with earlier FLE onset and longer FLE duration.[89]

2.4.2 Group Averages

In all groups and tasks, regions of activation were typical of fMRI motor studies.[90,91] Performing motor tasks recruits primary motor cortex contralateral to hand movement,[90] as confirmed by the present study (Figure 2.5). However, while activity of other motor regions (superior parietal, premotor, supplementary motor) was *more prominent* in the hemisphere contralateral to hand movement, ipsilateral activation was still observed (Figure 2.5). Interestingly, bilateral activation in participants with right FLE was so extensive during left handed tasks that it appeared similar to bimanual tasks. Indeed, these motor regions show increased bilateral activity during more complex tasks.[91] Left handed tasks were likely more complex for participants with right FLE because they primarily recruit the epileptic hemisphere. This same phenomenon was not observed in participants with left FLE; however, increased right hemisphere activity during bimanual finger-tapping could suggest greater compensatory reliance on the non-epileptic hemisphere.

2.4.3 Between Group Contrasts

2.4.3.1 Right FLE vs Controls

Greater activity in participants with right FLE was restricted to the left handed and bimanual coordination tasks (Figure 2.6 b). Under normal circumstances both of these tasks rely on the right (epileptic) hemisphere, whereas right handed tasks rely on the left (healthy) hemisphere. This suggests that normal recruitment of the epileptic hemisphere was insufficient to perform such tasks and that additional brain regions in the healthy hemisphere were recruited as a means of compensation. This contrasts the finger-tapping tasks (Figure 2.6 a), which had no additional recruitment presumably because of the simplicity of these tasks, rendering compensatory activity unnecessary for adequate performance. Regions of *less* activity in participants with right FLE were primarily localized to the right (epileptic) hemisphere presumably due to distant effects of the ipsilateral seizure focus. Decreased activation in distant cortex further highlights the extensive connectivity between the frontal lobe and other brain regions, and suggests that propagation of epileptic activity can affect interictal functioning of distant cortex.[7]

The posterior parietal cortex can be targeted for compensation (increased activity in the *left* hemisphere during bimanual and left handed coordination), and forfeited (decreased activity in the *right* hemisphere during all finger-tapping tasks), suggesting its functional flexibility. Posterior parietal cortex integrates sensory and motor information and is pivotal for synchronizing hand movements with external stimuli,[34] suggesting that it was likely activated in coordination tasks as a compensatory region.

During the bimanual coordination task, differences in activation suggest that participants with right FLE perceive greater task complexity. All three regions of increased activity in

participants with right FLE are implicated in error-detection,[92-95] and show increased activity during complex motor tasks when compared to simpler tasks.[94-96] The anterior cingulate and insula detect conflict processes;[92,93,97] and the superior temporal gyrus resolves conflict after detection.[94,95] This suggests that participants with right FLE make more errors, presumably due to the difficulty of the bimanual coordination task. Additionally, increased activity was observed in the superior temporal gyrus, which is activated during sequence processing tasks[98] such as the coordination task in this study. However, it shows less activation with increased practice,[99] suggesting that participants with right FLE had not mastered the task as well as control participants.

2.4.3.2 Left FLE vs Controls

Interpretation of results comparing left FLE to other groups was done with caution, as there were half as many participants. Unfortunately, differences between groups were observed in white matter regions and therefore likely artefact (Figure 2.7).

During finger-tapping tasks, participants with left FLE had significantly less activation in the default mode network (Figure 2.7 a). This occurred primarily during the bimanual task, similar to results in participants with right FLE (Figure 2.6 a). Default mode network suppression indicates increased focus to the external task,[25,39] suggesting that participants with FLE were more focus during bimanual finger-tapping tasks but not during unimanual tasks, likely because of the synchrony required between hands in bimanual tasks.

Decreases in right subcortical activity occurred in many tasks in participants with left FLE (Figure 2.7). Frontal lobes project ipsilaterally and contralaterally to subcortical structures[100] and previous studies demonstrated bilateral activation of the thalamus and putamen

during motor tasks.[100] Decreased activity in right subcortical structures could suggest less reliance on the non-dominant hemisphere, as all participants with left FLE were right handed.

2.4.3.3 Right FLE vs Left FLE

Overall, participants with right FLE exhibited significantly greater activity than those with left FLE in motor regions including bilateral premotor, prefrontal, and posterior parietal cortex (Figure 2.8). This is likely due to the disparity in participant numbers (i.e., many more participants with right FLE contributing to the results).

Participants with right FLE had significantly increased subcortical activation during both unilateral tasks, specifically in the putamen and thalamus. This suggests that subcortical motor projections are disrupted in participants with left FLE or enhanced in participants with right FLE. Said differences were observed *bilaterally* between groups differing only in seizure foci *lateralization*. Participants with left FLE had significantly poorer performance during the coordination task (see Table 2.4), which could reflect greater underlying *bilateral* network disruption.

The findings of the present study suggest that reliance on the epileptic hemisphere required greater focus on the task in participants with right FLE. There was greater suppression of the default mode network in participants with right FLE during left handed coordination, a task that requires recruitment of *right* hemisphere motor regions; the epileptic hemisphere in participants with right FLE and healthy hemisphere in those with left FLE. As mentioned previously, default mode network suppression indicates greater focus on the external environment.[25,39]

2.4.4 Within Group Contrasts: Coordination vs Finger-Tapping Tasks

Coordination and finger-tapping tasks evoke different cortical responses. The coordination task is more complex and activates additional brain regions.[80] This complexity permitted more precise targeting of motor impairments in individuals with epilepsy; all participants performed the finger-tapping task with ease.

Comparing bimanual tasks revealed the most differences (Figure 2.9 a). The coordination task was associated with greater suppression of the default mode network, suggesting that participants focused more during task performance.[101] During bimanual coordination greater activation occurred in motor-related regions, including posterior parietal cortex and premotor areas, which are involved in planning and regulating complex motor functions,[89] indicating the complex nature of the coordination task. Differences in activity appeared to be greater in controls than either epileptic group suggesting that finger-tapping and coordination tasks are more equally complex for participants with FLE, resulting in fewer differences between the two tasks.

Differences between unimanual coordination and finger-tapping are less robust (Figure 2.9 b,c). Difficulty levels are likely more similar between these tasks than between bimanual tasks; bimanual coordination requires different movements for each hand, rather than just a single movement of one hand. In the left handed coordination task participants with left FLE and controls exhibited greater right hemisphere activation, whereas those with right FLE showed bilateral activation (Figure 2.9 b). This reflects greater reliance on the healthy hemisphere for complex tasks in participants with right FLE. Alternatively, when comparing right handed tasks there was greater activation in left hemisphere motor regions in all groups (Figure 2.9 c). Bilateral activation was expected in participants with left FLE, as occurred in those with right

FLE during left handed comparisons. Either seizure lateralization did not affect both FLE groups similarly or left FLE numbers were not sufficient enough to evoke significant bilateral responses.

2.4.5 Relationship Between LIs and Seizure Demographic Factors

2.4.5.1 Number of Months Since Last Seizure

During the left handed coordination task in participants with right FLE, the left somatosensory cortex was more active in participants with recent seizures and less active in those that were relatively seizure free (Figure 2.10). This demonstrates greater activity in the hemisphere contralateral to typical left handed recruitment (healthy hemisphere), in a region that consistently demonstrates compensatory activation.[59,79]

During the right handed coordination task there were subtle and non-lateralizing differences in participants with left FLE when examining brain regions responsive to the period of seizure freedom (Figure 2.12). Perhaps individuals with left FLE recruit *different* compensatory ipsilateral motor regions following a seizure. Indeed, patients demonstrate additional recruitment of many regions including premotor, supplementary motor, and posterior parietal cortex.[59] Due to low numbers, if each participant relied on different brain regions for functional compensation these would not reach significance in group comparisons.

Overall, participants with both left and right FLE demonstrated significantly increased reliance on the healthy hemisphere with recent seizures, and regained reliance on the epileptic hemisphere with longer periods of seizure freedom (Figures 2.10 and 2.12). These findings are supported by studies examining motor recovery in stroke,[48,102] animal models of epilepsy,[21,62,103-105] and epilepsy surgery.[79] Patients with stroke lesions in or near the primary motor cortex initially had increased fMRI activation of ipsilateral motor regions from the affected hand.[56,57]

While activation of additional regions persisted over many months, there was an eventual return to pre-stroke activation patterns; i.e., there was less ipsilateral recruitment as the brain recovered from insults.[56,57] Additionally, an fMRI case study examined motor activation pre epilepsy surgery (multiple subpial transection), and again 7 and 13 weeks post surgery.[79] Activation remained constant across all three scans when finger-tapping with the unaffected hand.[79] However, tapping with the affected hand revealed increased activity in ipsilateral motor regions 7 weeks post surgery, then a return to presurgical levels at 13 weeks.[79] A study in rats reported similar temporary recruitment patterns, demonstrating a difference in motor activation 48 hours post seizure, but return to control patterns 1 week and 3 weeks post seizure.[103] All of these findings were analogous to observations in the present study (Figures 2.10 and 2.12), with *transient* increases in ipsilateral activation, but eventual recovery of normal activation patterns.

Furthermore, no correlation existed in participants with right or left FLE between LI of the contralateral (to seizure focus) task and period of seizure freedom. This is consistent with findings in stroke patients that demonstrated no temporal changes in brain activity when using the unaffected hand.[102]

2.4.5.1.1 Pathophysiology

The aforementioned studies proposed that due to the rapid changes in activation, reversibility of these changes, and distance of changes from the lesion site, it is likely that there are pre-existing but dormant motor systems in place[48,79] and less likely that new connections are forming to activate compensatory ipsilateral motor regions.[48,79] In fact, horizontal cortico-cortical connections exist between primary motor cortex and other motor regions in both ipsilateral and contralateral hemispheres.[48,105] If connections are inhibited under normal conditions, a lesion (or

perhaps recurrent seizures) could result in disinhibition,[48] initiating additional recruitment to maintain motor function. Indeed, patients with higher seizure frequencies have impaired cortico-cortical inhibition.[57] However, once normal conditions are reinstated (i.e., long period of seizure freedom), inhibition is re-exerted upon compensatory cortical regions and normal activation patterns resume.[48,79] This could explain why participants with FLE with recent seizures initially had increased recruitment of the non-epileptic hemisphere during coordination tasks (disinhibition), which decreased with longer periods of seizure freedom (inhibition re-exerted) (Figures 2.10 and 2.12).

Studies in rats also proposed the theory of disinhibition to explain a revealing of cortical motor maps.[62,103,105] Pre-existing cortico-cortical connections between motor regions are disinhibited by GABA antagonists, which results in additional motor recruitment.[106] Adjunct to this, kindling in rats amplifies NMDA receptor activation and increases presynaptic glutamate release, which also promotes additional motor recruitment.[107] This suggests that both GABA and glutamate transmission influence the ability to recruit additional motor regions through *pre-existing* cortico-cortical connections during task performance.[62]

The studies above focused on lesions very close to or within primary motor cortex, yet participants in the present study had seizure foci throughout the frontal lobe, many of which were distant to primary motor cortex. Hippocampal kindling in rats resulted in revealing of cortical motor maps, suggesting that similar effects occur due to seizure propagation.[62] Such mechanisms could explain changes in motor activation observed in participants with FLE that have lesions distant to primary motor cortex.

2.4.5.1.2 Laterality Indices

During left and right handed coordination tasks, some participants with right FLE, but none with left FLE, had LIs outside of the 'normal' control range. This could be because the longest period of seizure freedom in the left FLE group was ~30 months, while in the right FLE group it was ~110 months. Indices outside normal range signify greater suppression of the non-dominant (with respect to LI) hemisphere and greater activation of the dominant (with respect to LI) hemisphere. This suggests increased disinhibition in participants with recent seizures outside of the normal range (LI>+1), and increased re-exertion of inhibition in seizure free participants (LI<-1).

2.4.5.2 GTC Seizures in Past Year

Participants with right FLE with more GTC seizures in the past year had greater reliance on the left hemisphere when performing the left handed coordination task (Figure 2.11). This is similar to reports of higher seizure frequency causing increased ipsilateral (to hand movement) activation.[108] Despite a low number of participants experiencing GTC seizures in the past year (n=4), the compensatory region relied upon to perform the task was analogous to that observed in Figure 2.11, which is commonly recruited for functional motor compensation in patients.[59] It is also likely recruited by disinhibitory mechanisms.

2.5 Overall Conclusions

This was the first known study to examine fMRI motor activation in a group of adult participants with FLE. Significantly poorer performance scores were discovered during motor coordination tasks when comparing participants with FLE to controls. In participants with right FLE,

significantly greater ipsilateral (to hand movement) activation was observed during tasks that predominately recruit the epileptic hemisphere. However, differences in participants with left FLE were less conclusive likely due to low numbers. Additionally, in both FLE groups there was a relationship between the number of months since last seizure and LI of coordination tasks with hand movement contralateral to the seizure focus. There was an initial reliance upon the ipsilateral (to hand movement) hemisphere, and an eventual recovery of contralateral activation.

Research examining cortical plasticity in functionally critical brain regions highlights the importance of performing thorough pre-surgical investigations to minimize removal of eloquent brain tissue. This study not only demonstrated the flexibility of functional motor regions, but also the transient nature of this flexibility. The use of fMRI provided cortical maps with spatial resolution that currently surpasses other available non-invasive techniques.

Chapter Three: **Examination of Motor Networks using Resting-State fMRI**

3.1 Introduction

Resting-state activity of the brain accounts for over 50% of the brain's metabolic resources[65] and appears to be organized in the form of distinct, yet interacting networks.[64] These networks are hypothesized to develop, maintain, and increase the reliability of neural responses to external stimuli,[68,109] and can be studied using techniques such as fMRI. By using resting-state fMRI to examine brain networks, certain limitations that occur during task-based fMRI are overcome. In particular, the lack of a task enables individuals of all ages and abilities to participate, and additionally does not rely on accurate task performance.

Disruptions in resting-state networks have been observed in a number of neurological disorders and diseases, including amyotrophic lateral sclerosis,[110] stroke,[111] Parkinson's disease,[112] and multiple sclerosis.[113] It is generally believed that reduced connectivity between brain regions indicates network disruption, whereas increased connectivity implies recruitment of alternative resources as a mode of compensation.[69] Indeed, significantly lower connectivity within specific networks has been reported in patients with epilepsy. For example, patients with left TLE exhibit decreased connectivity within language networks compared to controls,[6] as well as reduced connectivity between the hippocampus and other brain regions.[70] These patients experienced language[6] and memory[70] deficits, suggesting that resting-state network disruption may underlie the behavioural deficits observed in patients with epilepsy.

Patients with FLE commonly exhibit motor impairments, including deficits in coordination, dexterity, and fine motor skills.[3] Currently, the source of these functional motor deficits is unknown. It was hypothesized that motor impairments seen in patients with FLE are

associated with resting-state network disruption, specifically within the motor network. To investigate this hypothesis, fMRI was used to examine resting-state motor network connectivity in participants with FLE. Findings from this project may lead to a better understanding of the mechanisms underlying functional motor deficits, and ultimately lead to better treatment and recovery options for patients with FLE.

3.2 Methods

This study was conducted during the same imaging session as the study described in Chapter Two.

3.2.1 Subjects

Participants were recruited as described in Chapter Two.

3.2.2 Participant Instructions and fMRI Data Acquisition

While in the scanner, participants were asked to remain awake and move as little as possible while focusing their attention on a central fixation cross displayed on a projector screen. Functional and structural MR images were acquired using the same scanner and imaging parameters as described in section 2.2.3. Functional MR data were collected for five minutes during subject rest. Of note, resting-state data were collected *following* the motor tasks described in Chapter Two.

3.2.3 Data Analysis

3.2.3.1 Pre-Processing of fMRI data

Pre-processing of images was completed using FSL (fMRIB Software Library; http://www.fmrib.ox.ac.uk/fsl/)[82] to correct for non-physiological variability in the data as described in section 2.2.4.2.

3.2.3.2 Determining Regions of Interest

In order to identify resting-state motor networks, brain connectivity was examined in relation to two regions of interest (ROI): the left and right sensorimotor cortices. Different ROI generation techniques can be used, two of which I explored. The first uses an anatomical atlas to identify ROIs and thereby ensures consistency of location across individuals. However, the exact location of functional tissue can vary between individuals, therefore the second technique locates ROIs based on active brain regions during motor task performance. Unfortunately, this second method may introduce confounding factors such as variability due to task performance. Because both of these methods have limitations, both were used to generate separate ROIs in every participant, and the ROIs were subsequently compared.

For the first technique I used the Harvard-Oxford cortical atlas[86] to identify the primary motor cortex (precentral sulcus – BA 4) and the primary sensory area (postcentral gyrus – BAs 3, 2, and 1), defined as extending from the lateral surface to the midline and from the vertex of the brain to the level of the superior aspect of the lateral ventricles caudally (Figure 3.1).[114] Both ROIs (left and right) were subsequently registered to each individual's functional space using FSL's FLIRT (FMRIB's Linear Image Registration Tool)[84] (average ROI size in functional space = 471 voxels). ROIs were trimmed using an inter-voxel cross-correlation technique, which

resulted in a single cluster of the 400 most temporally correlated voxels in terms of their resting-state BOLD signal.[115] The decision to trim ROIs to 400 voxels was based on the size of the smallest ROI in functional space prior to trimming. The second technique involved selecting the 400 most significantly activated voxels within each of the left and right sensorimotor cortices during the bimanual finger-tapping task.[115] Completing these techniques resulted in four ROIs for each individual: a right anatomical, left anatomical, right functional, and left functional.

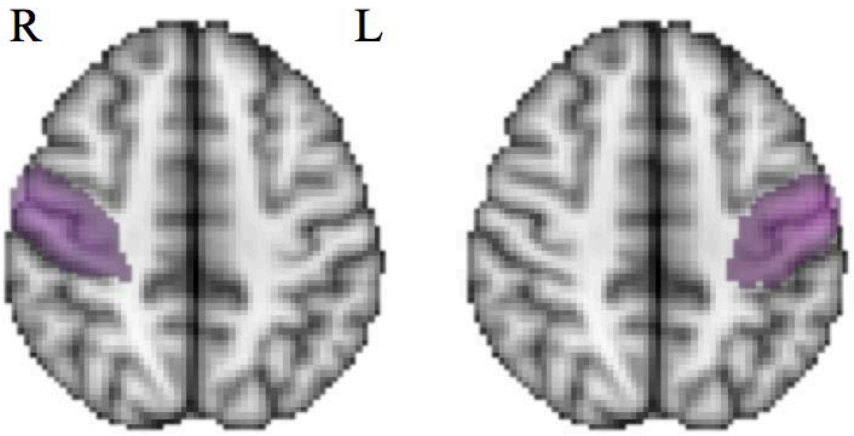


Figure 3.1 Anatomical masks drawn in standard space using the Harvard-Oxford atlas.

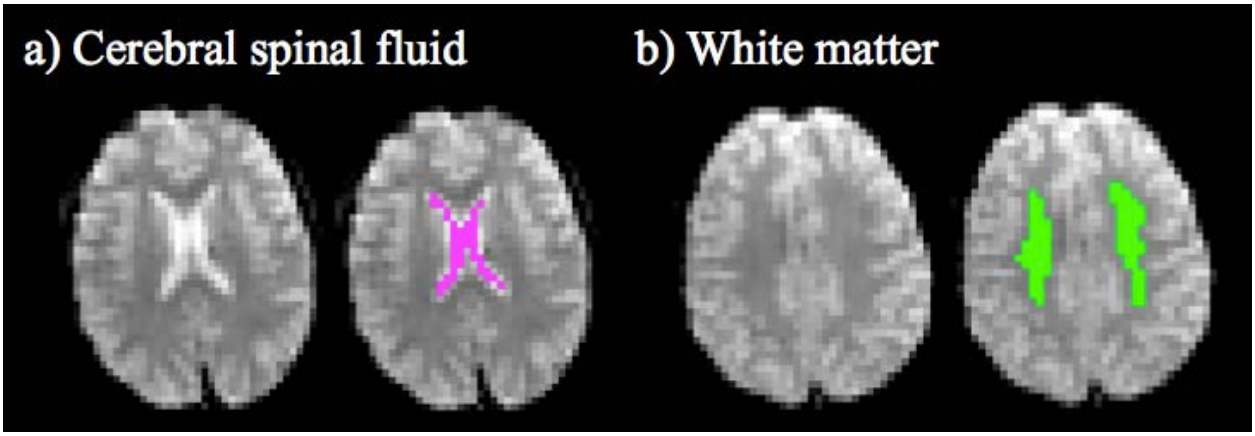
For every individual, the right anatomical and functional ROIs were compared, and the left anatomical and functional ROIs were compared. For each comparison, the difference between the center of mass, as well as correlation between the average BOLD signals time-course during resting-state was computed. ROIs were deemed sufficiently comparable if the center of mass was less than one voxel size (3.75 x 3.75 x 4mm) apart, and if the correlation between temporal BOLD signals was significant (significance calculated using Pearson's correlation coefficients).

The use of anatomical ROIs was preferred because there is more consistency across individuals. Additionally, this ROI identification technique did not rely on accurate task performance.

3.2.3.3 First-Level Analysis

Relative to task-based fMRI BOLD signals, resting-state fMRI BOLD signals are low amplitude. Therefore, BOLD signal from white matter, cerebral spinal fluid, and BOLD signal artefact due to motion were extracted from the data using a first-level GLM to remove excess noise (see section 2.2.4.3 for more information on FSL and first-level GLM analyses). Image voxels within each of the white matter and cerebral spinal fluid regions were selected by hand over the pre-processed functional data (Figure 3.2) and saved as a mask. The average BOLD signal time-course was taken for all voxels within the white matter and cerebral spinal fluid masks separately. These time-courses plus the six directional estimates of head displacement (i.e., translation and rotation in the x, y, and z directions) were entered into a first-level FEAT analysis as nuisance factors, and the resulting residual data were used for remaining analyses.

To determine brain regions that were functionally connected to each of the left and right sensorimotor cortices during rest, the average resting-state BOLD signal time-course for voxels in each ROI was entered as a model in a first-level FEAT analysis. This resulted in a voxel-wise estimate of BOLD signal correlation with the input model, thus providing an estimate of the strength of functional connectivity to the ROI (left or right sensorimotor cortex).



F**igure 3.2** Masks of a) cerebral spinal fluid, and b) white matter.

3.2.3.4 Higher-Level Analysis

After completing the individual first-level analyses, group analyses were conducted to obtain average connectivity maps for each ROI (right and left sensorimotor cortex) within each group (controls, right FLE, left FLE). These analyses were completed in FSL using FEAT, which implements the General Linear Mixed Model for higher-level analyses (see section 2.2.4.4).[82] Contrast images were also generated to compare differences in functional connectivity between groups and ROIs.

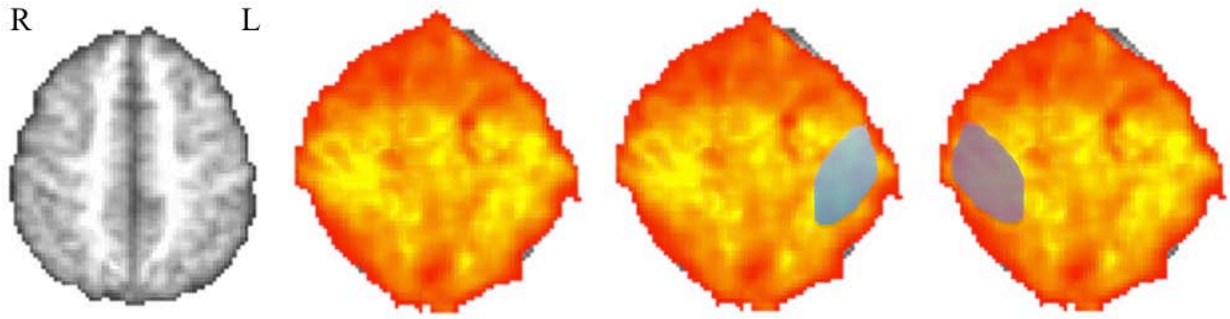
Maps were generated using a threshold of Z>3.1 for mean maps, Z>2.3 for contrast maps, and a corrected cluster significance of p=0.05. Final statistical images were constructed using AlphaSim, a program that corrects for family wise error rates.[85]

3.2.3.5 Relationship Between LIs and Seizure Demographic Factors

Two LIs were calculated individually for each participant: one for each of the left and right sensorimotor cortex connectivity maps. For more information on LI calculations refer to section

2.2.4.5. In this study, however, LIs were calculated relative to the right and left sensorimotor cortices, rather than the entire hemisphere (Figure 3.3). Sensorimotor cortex masks that were chosen to calculate LIs were the same as the ROIs used for first-level FEAT analyses (see section 3.2.3.2).

A Spearman correlation analysis was performed to determine if there was an association between LIs and each seizure demographic factor for participants with right and left FLE. Seizure demographics included age at epilepsy diagnosis, years since diagnosis, lifetime seizures (total/GTC seizures), seizures in past year (total/GTC seizures), and the number of months since the participant's last seizure.



$$LI = \frac{(\#\text{ voxels L})(\text{Z-score L}) - (\#\text{ voxels R})(\text{Z-score R})}{(\#\text{ voxels L})(\text{Z-score L}) + (\#\text{ voxels R})(\text{Z-score R})}$$

5. Calculate laterality index

Figure 3.3 Example of laterality index calculation using sensorimotor cortex masks.

3.3 Results

3.3.1 Subjects

In total, 21 participants were recruited: 7 with right FLE, 6 with left FLE (Table 3.1), and 9 controls (4 males) with a mean age of 29.9 ± 13.0 (range: 16-57).

Table 3.1 Patient demographics.

Gender	Age at scan	Age at epilepsy onset	Seizure burden	Months since last seizure	Seizure focus	Seizure types
Participants with Right FLE						
M	16	7	Low	7	Supplementary sensorimotor	GTC, CP
F	20	12	Moderate	0	Primary motor	GTC, CP, SP
M	32	26	Moderate	14	Anterior frontopolar	SP
M	33	28	Low	20	Anterior frontopolar	CP
F	36	0	Low	10	Supplementary sensorimotor	GTC, CP
M	46	39	Low	13	Anterior frontopolar	GTC, CP
M	47	28	Low	112	Supplementary sensorimotor	GTC
5M/2F	**32.9 ± 11.8**	**20.0 ± 13.9**		**25.1**		
Participants with Left FLE						
M	19	4	Low	6	Supplementary sensorimotor	GTC, CP, SP
M	28	2	Very high	2	Primary motor	GTC, CP, SP
M	30	8	High	0	Primary motor	GTC, SP
M	39	2	Very high	1	Dorsolateral	GTC, CP
F	55	12	Low	18	Primary motor	GTC, SP
F	65	41	Low	30	Primary motor	CP, SP
4M/2F	**39.3 ± 17.5**	**11.5 ± 15.0**		**9.5**		

3.3.2 ROI Determination

Distances between the centers of mass of anatomical and functional left and right ROIs were all within a one-voxel range (fMRI voxel dimensions: 3.75 x 3.75 x 4mm) (Table 3.2). There was a significant correlation ($p<0.05$) between temporal BOLD signal time-courses of anatomical and functional ROIs in all three groups (Table 3.3). Given these results, it was determined that there would not be a significant difference in connectivity maps between methods,[115] therefore all subsequent analyses were performed using ROIs based on the anatomical method in order to maximize consistency across all individuals.

Table 3.2 Distance between centers of mass of anatomical and functional masks.

Group	Right		Left	
	Mean ± Std Dev (mm)	*Range (mm)*	*Average ± Std Dev (mm)*	*Range (mm)*
Controls	0.877 ± 0.354	0.272 – 1.302	0.806 ± 0.248	0.305 – 1.103
Right FLE	2.563 ± 0.278	0.337 – 2.875	1.565 ± 0.345	1.193 – 1.875
Left FLE	2.188 ± 0.227	2.028 – 2.349	2.196 ± 0.327	1.965 – 2.428

Table 3.3 Correlation between BOLD signal time-courses of anatomical and functional masks.

Group	Right		Left	
	Mean ± Std Dev (r^2)	*Range (r^2)*	*Average ± Std Dev (r^2)*	*Range (r^2)*
Controls	0.996 ± 0.002	0.992 – 0.999	0.994 ± 0.004	0.986 – 0.998
Right FLE	0.940 ± 0.011	0.928 – 0.951	0.958 ± 0.016	0.940 – 0.972
Left FLE	0.921 ± 0.030	0.900 – 0.942	0.944 ± 0.022	0.930 – 0.961

3.3.3 Group Average Images

Figure 3.4 shows the average left and right sensorimotor connectivity maps for each group (controls, right FLE, left FLE). Brain regions that demonstrated significant connectivity in both connectivity maps (left and right ROI) and in all three participant groups included the contralateral sensorimotor cortex, supplementary motor area, premotor cortex, insula, medial prefrontal cortex, and thalamus (Figure 3.4). Additionally, control and right FLE groups displayed connectivity between the ROIs and the posterior cingulate, transverse temporal gyrus, lateral occipital cortex, and putamen. Relative to both ROIs, participants with left FLE had smaller regions of connectivity and lower correlations (Z-scores) when compared to participants with right FLE and controls.

3.3.4 Between Group Contrast Images

Figure 3.5 shows the statistical comparison between each of the three groups for both the left and right sensorimotor connectivity maps. Overall, participants with left and right FLE had decreased connectivity between the ROI and other brain regions when compared to controls; no brain regions showed increased connectivity (Figure 3.5). Specifically, in both connectivity maps participants with FLE exhibited decreased connectivity from the ROI to the insular, temporal, supramarginal, inferior parietal, and bilateral sensorimotor cortices. Additionally, participants with right FLE had reduced connectivity between the left and right ROI and the left lateral occipital cortex and putamen. No significant differences were observed between right and left FLE groups.

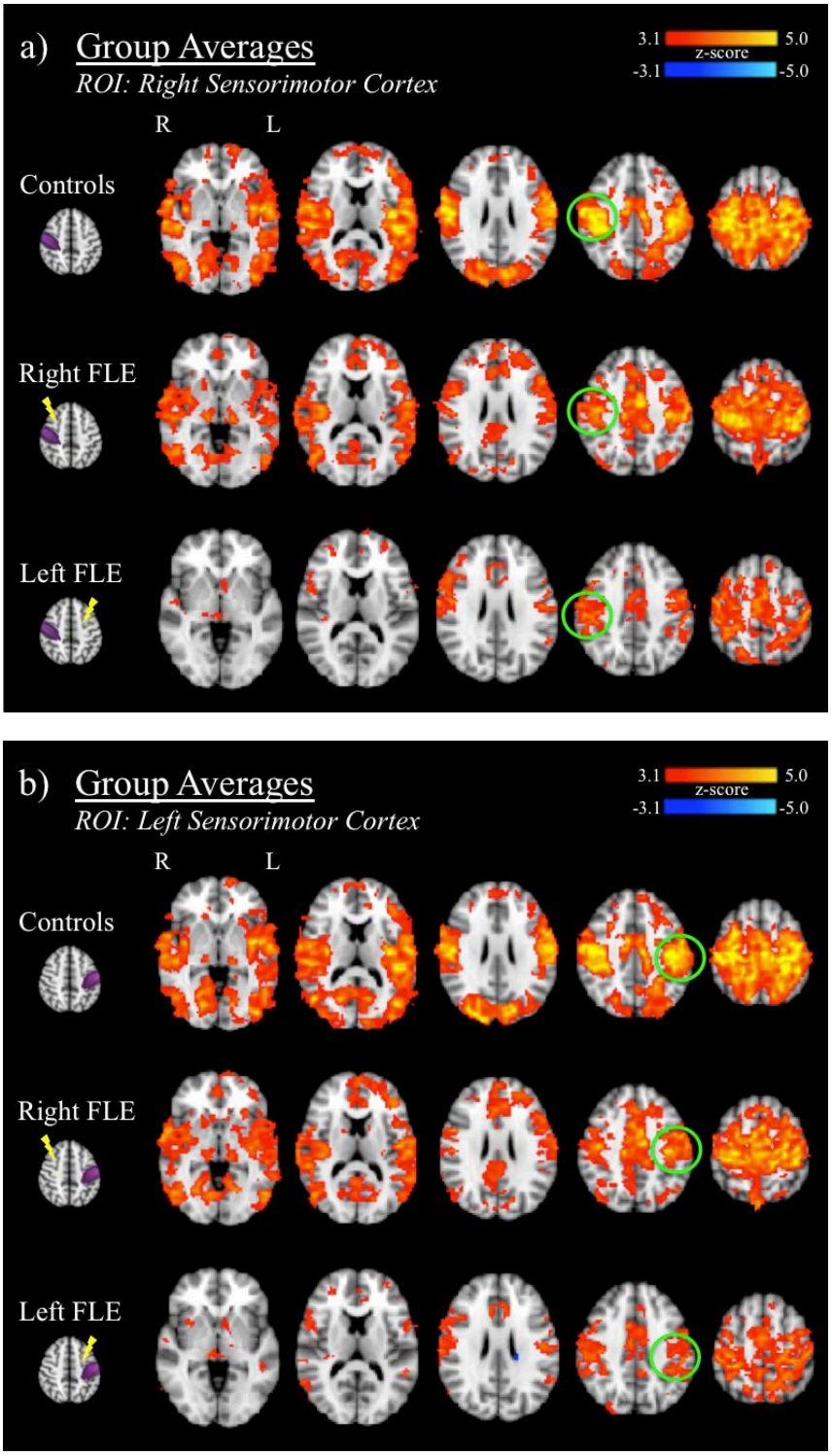


Figure 3.4 Group averages for a) right sensorimotor and b) left sensorimotor connectivity maps. Anatomical images in the inset on the left show the location of the ROI (purple shading) and the side of seizure foci for the group (lightning bolt). The green circle on the functional images shows the approximate location of the ROI.

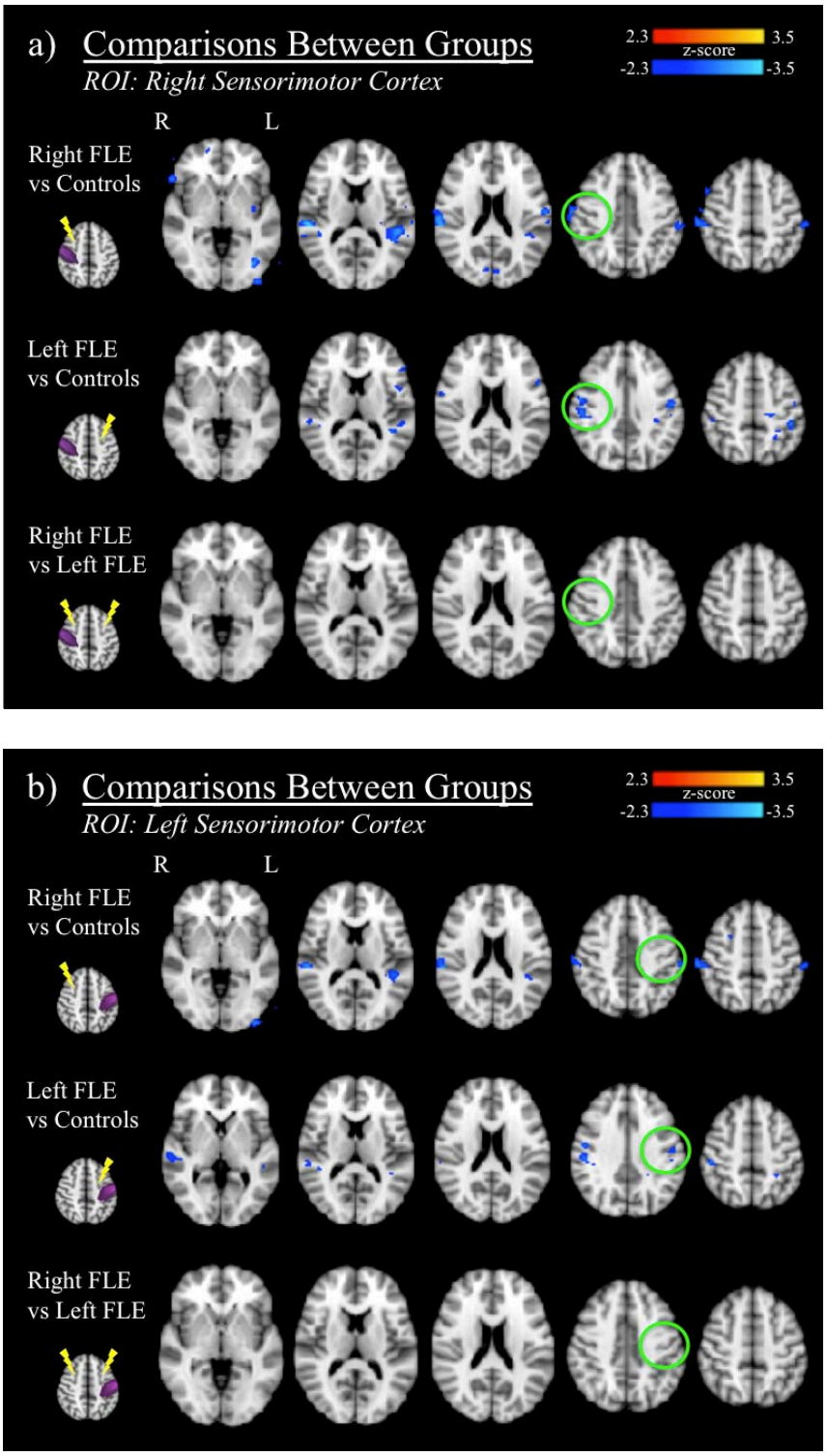


Figure 3.5 Comparison between groups for a) right and b) left sensorimotor connectivity maps. Red areas indicate regions *more* connected to the ROI and blue areas indicate regions *less* connected to the ROI in participants with FLE (for right/left FLE vs controls) or right FLE (for right vs left FLE).

3.3.5 Relationships Between LIs and Seizure Demographic Factors

Control participants had an average LI of 0.00 (range = -0.06 to 0.05) for the left connectivity map, and an average LI of -0.06 (range = -0.14 to 0.01) for the right connectivity map.

3.3.5.1 Participants with Right FLE

In participants with right FLE no significant correlations existed between LIs (in both right and left sensorimotor connectivity maps) and years since diagnosis, lifetime GTC seizures, seizures in past year (total/GTC seizures), or number of months since last seizure. However, LIs calculated from the left sensorimotor map (ROI contralateral to the seizure focus) were negatively correlated to participants' age at diagnosis (Figure 3.6) and positively correlated to participants' total number of lifetime seizures (Figure 3.7). Six out of seven participants with right FLE had LIs above (more positive than) the control LI range (range = -0.06 to 0.05) in the left connectivity map.

3.3.5.1.1 Age at Epilepsy Diagnosis

Participants diagnosed with epilepsy at a younger age had decreased connectivity between the left and right sensorimotor cortex compared to participants diagnosed at a later age (Figure 3.6). The participant that was diagnosed at age 40 had an LI near 0, which is consistent with the highest degree of synchrony between the left and right sensorimotor cortex. Therefore, epilepsy diagnosed at a later age appears to correspond with greater connectivity between bilateral sensorimotor cortices.

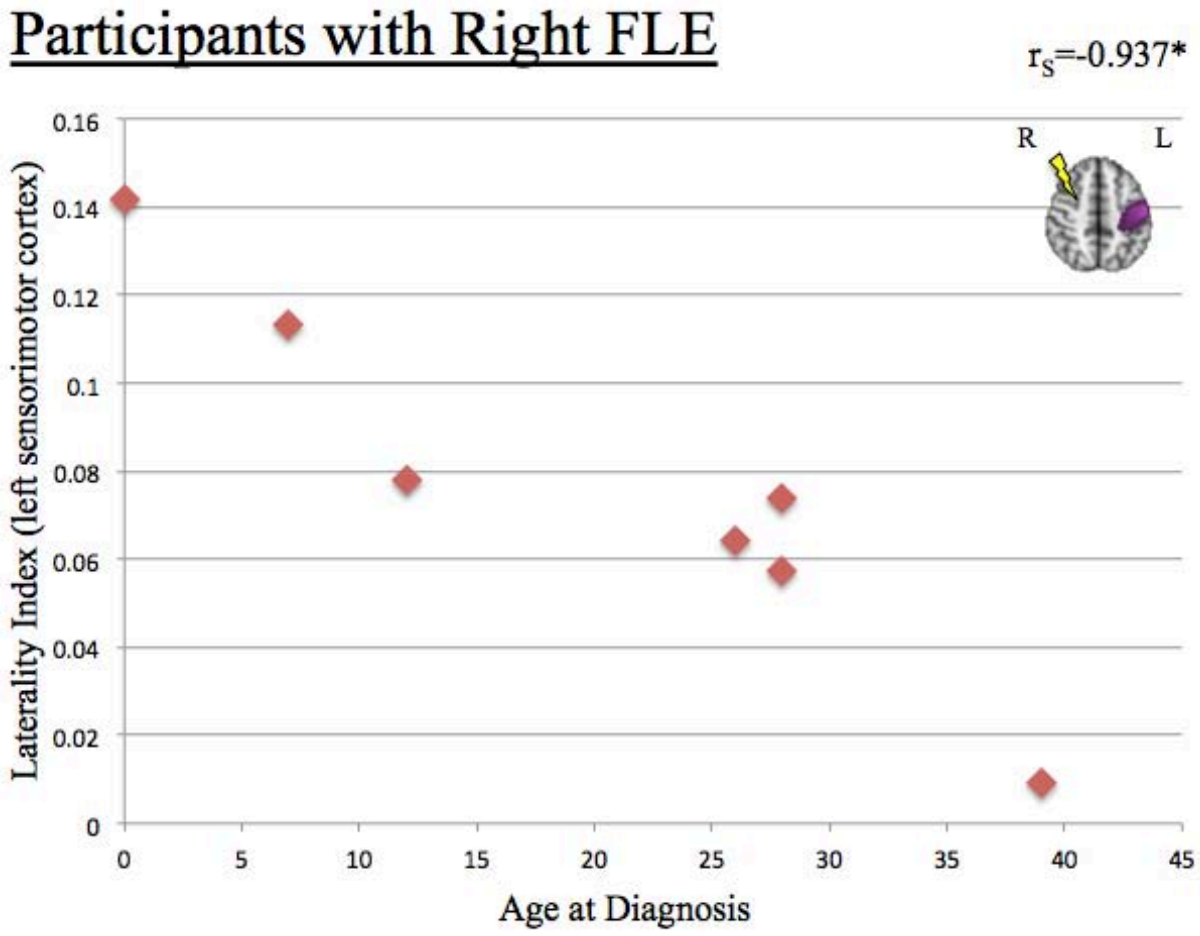


Figure 3.6 Relationship between laterality indices from the left sensorimotor connectivity map and age at diagnosis in participants with right FLE. Spearman's rank correlation coefficient is in the top right hand corner. Positive laterality indices indicate *less* connectivity from the left sensorimotor cortex to the right sensorimotor cortex, negative laterality indices indicate *greater* connectivity between the left and right sensorimotor cortices. The anatomical image on the top right shows the location of the ROI (purple shading) and the side of seizure foci for the group (lightning bolt).

3.3.5.1.2 Total Lifetime Seizures

Participants with few lifetime seizures had greater functional connectivity between the left and right sensorimotor cortex (Figure 3.7). With more lifetime seizures, connectivity of the right sensorimotor cortex to the left sensorimotor cortex decreased.

3.3.5.2 Participants with Left FLE

Significant correlations were not found between most seizure demographics and LIs (in both connectivity maps) in participants with left FLE. However, LIs calculated from the right sensorimotor map (ROI contralateral to the seizure focus) were negatively correlated to the total number of lifetime seizures (Figure 3.8). This same relationship, with respect to the seizure focus, was observed in participants with right FLE (Figure 3.7). Three out of six participants with left FLE had LIs below (more negative than) the control range (range = -0.14 to 0.01) in the right connectivity map.

3.3.5.2.1 Total Lifetime Seizures

Figure 3.8 shows the correlation between LIs calculated using the right sensorimotor connectivity map and the total number of lifetime seizures in participants with left FLE. Individuals with very few lifetime seizures had stronger functional connectivity between the right and left sensorimotor cortex. However, with a greater number of lifetime seizures this connectivity decreased.

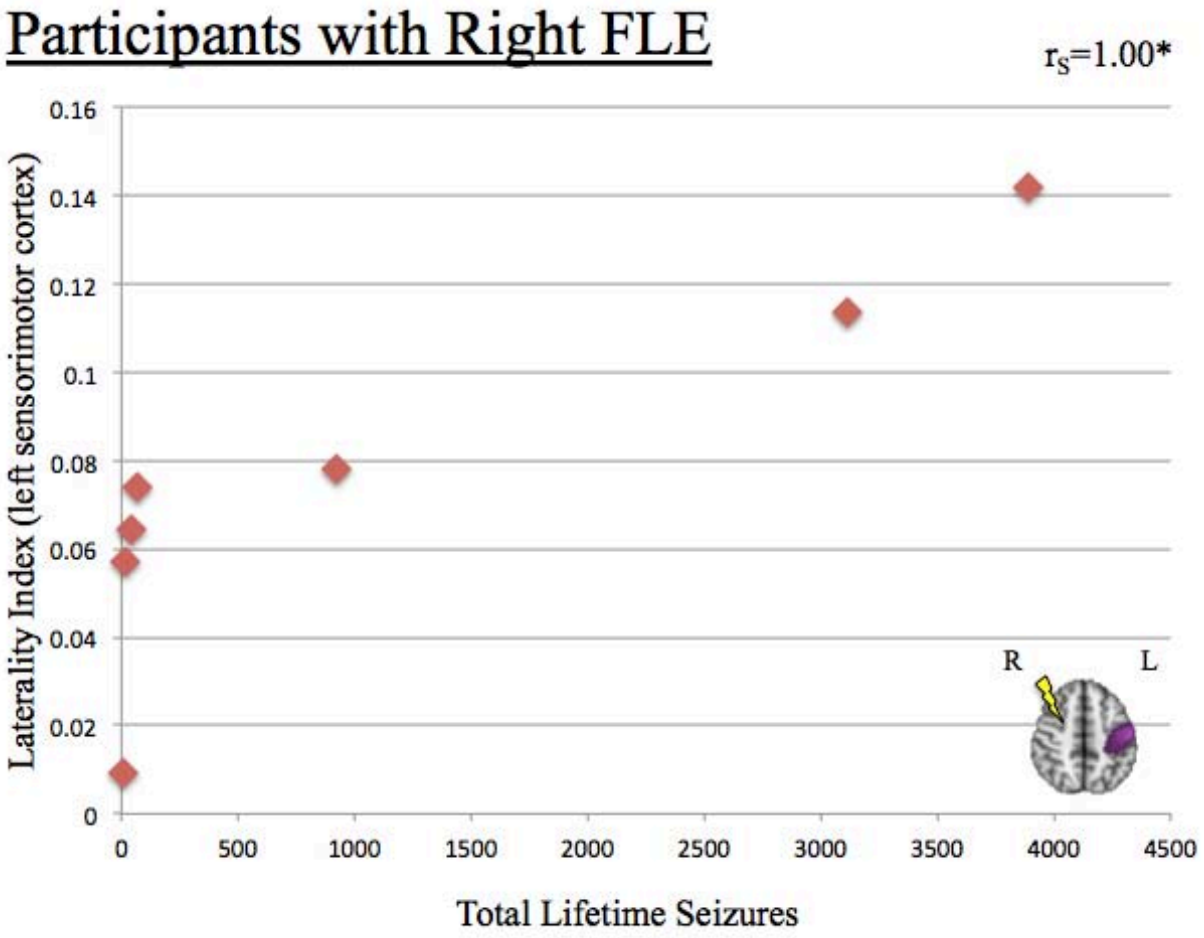


Figure 3.7 Relationship between laterality indices from the left sensorimotor connectivity map and total number of lifetime seizures in participants with right FLE. Spearman's rank correlation coefficient is in the top right hand corner. Positive laterality indices indicate *less* connectivity from the left sensorimotor cortex to the right sensorimotor cortex, negative laterality indices indicate *greater* connectivity between the left and right sensorimotor cortex. The anatomical image on the bottom right shows the location of the ROI (purple shading) and the side of seizure foci for the group (lightning bolt).

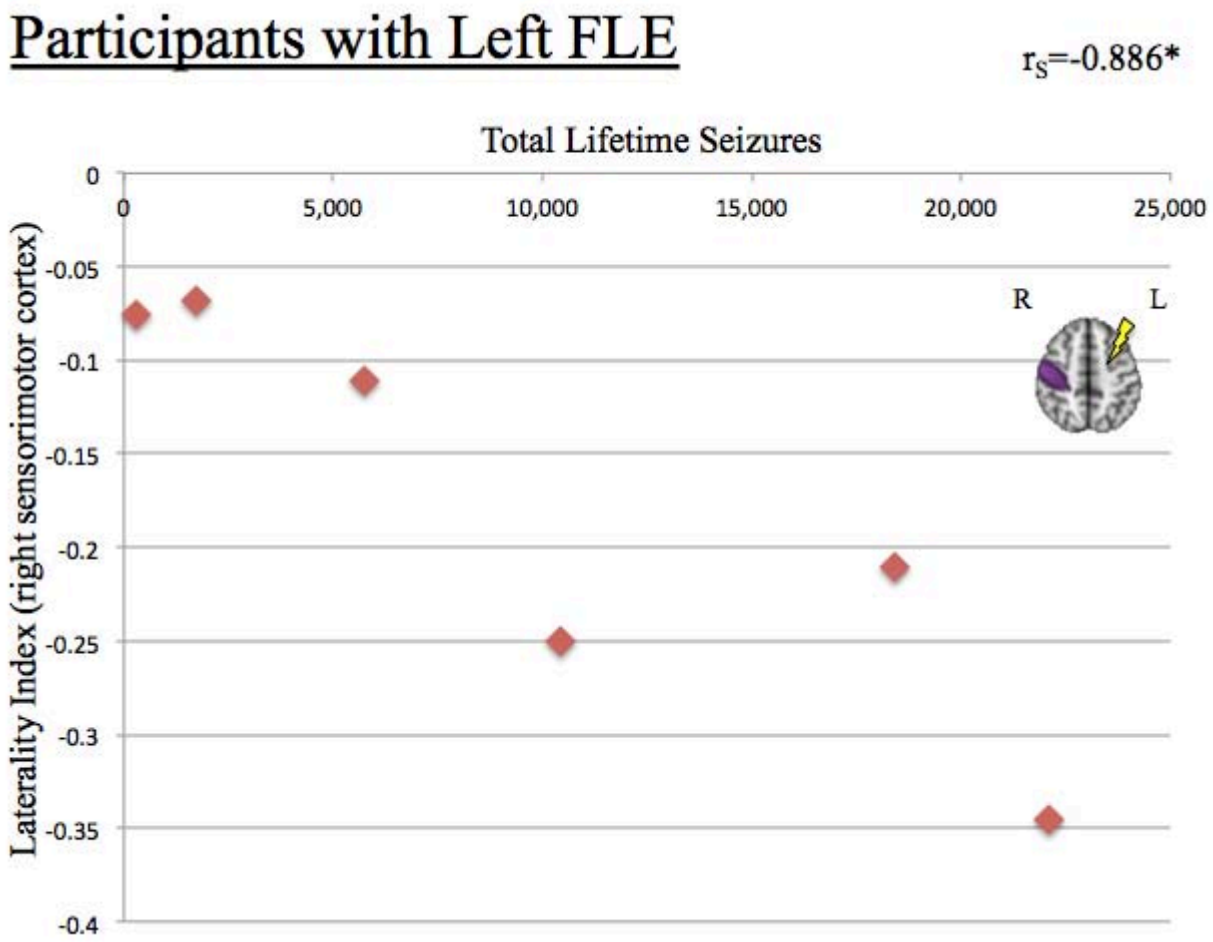


Figure 3.8 Relationship between laterality indices from the right sensorimotor connectivity map and total number of lifetime seizures in participants with left FLE. Spearman's rank correlation coefficient is in the top right hand corner. Positive laterality indices indicate *less* connectivity from the right sensorimotor cortex to the left sensorimotor cortex, negative laterality indices indicate *greater* connectivity between the right and left sensorimotor cortex. The anatomical image on the top right shows the location of the ROI (purple shading) and the side of seizure foci for the group (lightning bolt).

3.4 Discussion

3.4.1 Group Average Images

3.4.1.1 Connectivity in Motor Regions

All three groups demonstrated connectivity between both ROIs and the contralateral sensorimotor cortex, supplementary motor area, and premotor regions (Figure 3.4). This is consistent with the results of previous studies that examined resting-state connectivity in motor networks.[116,117] Motor regions likely demonstrated strong functional connectivity because of their existing structural connections; the left and right sensorimotor cortices are joined by abundant cortico-cortical white matter projections through the corpus callosum.[118] These connections, structural and functional, are crucial for the coordination of left and right motor movements.[119]

3.4.1.2 Subcortical Connections

Subcortical regions that were functionally connected to both ROIs (Figure 3.4) are likely part of a subcortical motor circuit. A previously identified resting-state motor network consisting of subcortical regions included the thalamus, pallidum, putamen, and transverse temporal gyri.[120] Control and right FLE groups displayed connectivity to all of these regions in both ROI maps, except for the pallidum. Of these regions, the left FLE group only demonstrated connectivity between the ROIs and the thalamus, likely due to a low number of participants.

In general, the basal ganglia are involved in a variety of functions, each sub-served by its own network. For example, sensorimotor functions are executed through the motor circuit, in which the supplementary motor area, premotor, primary motor, and somatosensory cortex all provide input to the putamen.[120] The putamen then sends information to the thalamus by way of

the pallidum and substantia nigra, and output is directed primarily to the supplementary motor area.[120] The putamen and thalamus are the main input and output centres, and accordingly demonstrate functional connectivity to both ROIs in the results of the present study (Figure 3.4).

3.4.1.3 Additional Regions of Connectivity

Occipital, insular, posterior cingulate, and medial prefrontal cortex are *not* brain regions that usually demonstrate functional connectivity within resting-state motor networks; however, connectivity of these regions to both ROIs was observed in the present study (Figure 3.4). A study by Grigg *et al.*[121] compared resting-state networks pre- and post-task performance, and discovered resting-state connectivity patterns similar to the results of the present study *after* a motor task was performed. In *pre*-task resting-state data, the posterior cingulate cortex was functionally connected to other default mode network regions, as expected.[121] However, in *post*-task resting-state data, the posterior cingulate temporally fluctuated its connectivity between two networks: 1) the default mode network, and 2) the task-positive network (includes regions commonly activated during task performance).[121] Post-task connectivity to the task-positive network was *not* due to residual processing of the motor task; previous studies have demonstrated that baseline resting-state connections are rapidly restored following task performance.[122] Instead, the post-task interaction of connectivity between two networks was suggested to reflect a learning consolidation phase.[121]

Regions in the task-positive network included the pre- and post-central gyrus, supplementary motor area, insula, occipital cortex, putamen, thalamus, and superior temporal gyrus,[121] all of which were observed in the results of the present study (Figure 3.4). Additionally, the default mode network included the posterior cingulate and medial prefrontal cortex,[121] which

were also observed (Figure 3.4). Because resting-state data was collected after the motor task, it is possible that results of the present study demonstrated connectivity patterns including both the default mode network and task-positive network.

3.4.2 Group Contrast Images

3.4.2.1 Differences Between Participants with FLE and Controls

Compared to controls, both FLE groups demonstrated less functional connectivity between motor regions including sensorimotor cortex, posterior parietal cortex, and subcortical motor structures (Figure 3.5). Patients with brain tumours,[123] stroke,[111] amyotrophic lateral sclerosis,[110] and Parkinson's disease,[112] exhibit decreased connectivity in analogous regions. Interestingly, all of these neurological conditions are associated with motor impairments, similar to daily motor deficits experienced by patients with FLE.

3.4.2.1.1 Behavioural Motor Impairments

Participants with FLE demonstrated decreases in functional connectivity between bilateral sensorimotor regions (Figure 3.5), as well as poorer performance scores on coordination tasks (Table 2.4) when compared to controls. It is possible that this was a causal relationship. Indeed, associations exist between decreased motor network connectivity and functional motor impairments in neurological conditions, as demonstrated in patients with frontal and parietal brain tumours[123] and aging populations.[124] This association has also been demonstrated in epilepsy; reduced connectivity in memory networks of patients with TLE was positively correlated to poorer memory test scores.[70] Additionally, patients with TLE had decreased connectivity in language networks, providing an explanation for their functional language

deficits.[6] Given the findings of these studies, it seems plausible to speculate that decreased connectively in motor networks may be related to, at least in part, the motor deficits experienced by participants with FLE.

Additionally, decreased connectivity was observed between the sensorimotor cortex and supramarginal gyri in participants with FLE. This may suggest an inability to learn and perform motor tasks as effectively as controls because increased connectivity between these regions occurs following motor learning.[125] Overall, the present study demonstrated a reduction in functional connectivity between sensorimotor cortices and both local and distant brain regions (Figure 3.5). Previously studies showed that patients with FLE exhibit overall decreased connectivity between the entire frontal lobe and other brain regions, which was related to cognitive and motor impairments.[73]

3.4.2.2 Differences Between FLE Groups

There were no significant differences in either ROI maps between participants with right and left FLE (Figure 3.5). Additionally, there were no significant differences in motor performance scores between these two groups (Table 2.4). This further emphasizes that a relationship may exist between motor network connectivity and behavioural motor function. These results may also suggest that left and right FLE affects motor network connectivity in a similar manner.

3.4.2.3 Pathophysiology of Altered Resting-State Connectivity

A number of explanations for resting-state connectivity changes in patients with epilepsy have been proposed. These include an imbalance between neuronal excitation and inhibition, effects of interictal discharges, and network disturbances due to brain atrophy.

3.4.2.3.1 Excitation and Inhibition

Epilepsy has been characterized as an imbalance between excitation and inhibition.[6,126] Enhancement of inhibitory synaptic processes occurs to suppress seizure activity; this inhibition could affect other brain networks, likely those closest to the seizure focus.[6] Seizure foci within the frontal lobe (i.e., FLE) are close to primary regions involved in motor networks, thereby introducing the possibility of causing reductions in motor network connectivity. However, participants with seizure foci located *directly* within motor network regions may experience greater network disruption, and may therefore drive the observed differences between control and FLE groups. It would be beneficial to recruit additional participants in order to form separate groups based on more specific seizure foci location.

3.4.2.3.2 Interictal Discharges

Interictal discharges occur more frequently during periods of *rest*,[127] and these discharges are postulated be a source of decreased resting-state connectivity.[6] In fact, interictal discharges can propagate through existing fibre tracts and connect their source with other brain regions, ultimately impacting large networks.[128] Studies examining resting-state networks in patients with idiopathic generalized epilepsy observed a decrease in functional connectivity between the basal ganglia and cortical motor structures (specifically the supplementary motor area), which positively correlated with the number of interictal discharges during scan time (EEG-fMRI); i.e., a greater number of discharges was related to a greater decrease in functional connectivity.[129] In our study, interictal discharges during scans may have caused decreased connectivity in resting-state motor networks. Studies using simultaneous EEG-fMRI recordings would help elucidate these findings.

3.4.2.3.3 Brain Atrophy

White and grey matter degeneration may have caused decreased connectivity in participants with FLE. Indeed, patients with FLE have shown frontal lobe atrophy both ipsilateral and contralateral to the seizure focus,[130,131] as well as decreased volume and increased diffusivity in the entire corpus callosum.[132] More specifically, these abnormalities were amplified in callosal regions connecting the seizure focus to the contralateral hemisphere.[132] Patients with TLE demonstrate a relationship between hippocampal atrophy and disrupted functional connectivity.[133] If a similar phenomenon were present in participants with FLE in the present study (i.e., abnormalities in white matter connections or grey matter atrophy), this too could result in decreased functional connectivity.

3.4.3 Relationship between LIs and Seizure Demographic Factors

In healthy adults there is generally a strong association between the left and right sensorimotor cortex, and therefore a high degree of correlation during resting-state. Ideally, the LI between these regions should be 0 indicating no hemispheric dominance. A shift in LI suggests that one hemisphere is acting more dominantly. Six participants with right FLE had LI values favouring the left hemisphere in the left connectivity map (above the control range), and three participants with left FLE had LI values favouring the right hemisphere in the right connectivity map (below the control range). Both groups demonstrated a reliance on the healthy hemisphere and decreased connectivity to the epileptic hemisphere, presumably due to the effects of seizure activity on resting-state networks.

3.4.3.1 Total Lifetime Seizures

In both FLE groups, connectivity between the sensorimotor cortices in the healthy hemisphere and the epileptic hemisphere decreased as the number of lifetime seizures increased (Figures 3.7 and 3.8). Previous studies have demonstrated decreases in the cortical volume of the frontal lobes and increases in callosal diffusivity in patients with longer FLE duration.[132] As mentioned previously, brain atrophy has been associated with decreased connectivity.[133] However, in the present study a relationship between epilepsy duration and degree of connectivity was not found. This may suggest that the total amount of seizure activity has a greater impact on functional connectivity in this study's FLE group. Alternatively, the group size may have been too small to observe a significant correlation with FLE duration.

Additional studies showed that epilepsy duration was related to connectivity decreases in patients with absence epilepsy[134] and generalized tonic clonic seizures,[69] but no correlation was present in children with medically refractory epilepsy.[135] Different relationships exist in all of these studies likely due to the heterogeneity of patients and networks examined. These disagreements may also highlight the unique presentation of each epilepsy syndrome and the inconsistent effects of seizures and epilepsy syndromes on brain networks. These studies also stress the need to examine homogeneous populations and similar networks.

3.4.3.2 Age at Epilepsy Diagnosis

Participants' age at epilepsy diagnosis and sensorimotor cortex connectivity were positively correlated in participants with right FLE (Figure 3.6). In patients with FLE, studies have demonstrated structural abnormalities in the brains of those with earlier lesions and earlier seizure onset. Specifically, abnormalities included reduced cortical size in frontal regions[136] and

impaired callosal inter-hemispheric connections,[132] likely due to disruptions of normal brain development. As discussed previously, structural connections can influence functional connectivity.[133] These studies provide evidence for impaired functional connectivity coinciding with earlier seizure onset. Furthermore, the development of functional connectivity in motor networks persists into adolescence[109] and these networks continue to change throughout life in response to environmental factors (e.g., learning).[17,125] This renders seizure onset at any age capable of interfering with normal development and maintenance of brain networks.

3.5 Overall Conclusions

The present study compared resting-state motor networks between participants with FLE and controls. FLE groups had reduced connectivity between left and right sensorimotor regions, and this reduction was exacerbated in participants with a greater number of lifetime seizures, as well as an earlier age at right FLE onset.

One limitation of this study was participant heterogeneity. Previous studies have demonstrated differences in resting-state connectivity depending on seizure foci location, age at epilepsy onset, epilepsy duration, and many other factors. Due to small numbers, participants were not divided into subgroups that were of an adequate size to examine these differences in greater detail.

Studies examining functional resting-state connectivity provide insights into the effects of epilepsy on normal brain function, effects that may lead to alterations in behavioural performance. Previous studies have demonstrated the ability of this method to predict the seizure onset zone[76] and functional post-surgical deficits[77] in patients with epilepsy. It is hoped that with future research, similar predictive values will be available specifically for patients with FLE.

Chapter Four: **Overall Discussion**

4.1 Introduction

Previous chapters focused on findings specific to each method: task-based or resting-state fMRI. This chapter explores potential explanations for these findings collectively and discusses limitations that may have affected the results. Additionally, possible future directions are discussed along with their implications on clinical procedures.

4.2 Comparison of Chapters Two and Three

Previous studies elucidated a relationship between increased resting-state connectivity amongst specific brain regions and high response magnitudes during tasks that evoke such regions.[137] Contrarily, in this research participants with right FLE exhibited increased activation during certain complex motor tasks, yet decreased connectivity in resting-state motor networks when compared to controls. Perhaps the additional recruitment during tasks supported the formation of new resting-state connections, while connectivity within typical motor networks declined.

The present study also demonstrated similarities between motor regions that were recruited during task performance and those that were involved in resting-state networks. Indeed, resting-state motor networks constitute brain regions that typically interact during motor task performance.[137,138] Additionally, participants with left and right FLE demonstrated decreased response magnitudes in motor regions during select motor tasks, as well as decreased functional connectivity between motor regions during resting-state. Because decreases in activity and connectivity were observed in motor regions using each method, this suggests that task and resting states may be affected in a similar way by frontal lobe seizure activity.

While LIs of complex motor tasks conveyed hemispheric dominance during task-induced brain activation, LIs of resting-state connectivity maps reflected the interconnectivity between left and right sensorimotor regions. LIs in each method (task-based and resting-state) were correlated with different seizure demographic factors. Patients with longer periods of seizure freedom relied less upon healthy hemisphere brain regions and more actively recruited the epileptic hemisphere during complex motor tasks. This correlation between period of seizure freedom and hemispheric dominance developed within a period of months. Additionally, participants with right FLE relied more heavily upon the healthy hemisphere during task performance when they had experienced more GTC seizures in the past year. Alternatively, resting-state connectivity revealed decreased synchrony between the left and right sensorimotor cortices with a greater number of lifetime seizures. Decreased resting-state connectivity was also present in participants with right FLE in relation to age at epilepsy onset; participants with earlier onset had less communication between bilateral sensorimotor cortices.

In summary, LI changes during task-performance were discernible between participants when examining seizure demographic factors that developed within a period of months, whereas resting-state changes were related to more long-term seizure demographic factors. Chapter Two discussed the possibility of pre-existing networks becoming disinhibited to recruit alternative cognitive resources during task-performance. This theory may represent a temporary phenomenon in response to external stimuli, a phenomenon that must occur repeatedly over time in order to establish reliable and concrete intrinsic resting-state networks that include analogous motor regions.

4.3 Limitations

Variability exists in individual presentations of epilepsy disorders, which can alter results between participants. Therefore, not only were the effects of left and right FLE examined, but the effects of these additional variables were examined as well.

Hermann *et al.* examined possible sources of variability in patients with epilepsy and organized them into three general categories.[89,139] The first category consisted of neurobiological factors that included pathology and etiology of the epileptogenic region, precise seizure foci locations, type of seizure, age at onset, duration of disorder, and frequency of seizures. The second category was comprised of psychosocial factors including psychological comorbidities of epilepsy. The third category focused on anti-epileptic drugs because of their effects on neurotransmitter activity and other metabolic functions.

4.3.1 Neurobiological Factors

Both Chapters Two and Three explored the effects of many seizure demographic factors on changes in task-based and resting-state fMRI. These factors included seizure type, age at epilepsy onset, epilepsy duration, and seizure frequency, some of which correlated with changes in the results of both fMRI studies. Differences were observed with respect to months since last seizure and number of GTC seizures in task-based fMRI data, as well as total number of lifetime seizures and age at epilepsy onset in resting-state fMRI data. These are similar to findings in previous studies (see section 2.4.5 and 3.4.3).

Additionally, results can vary depending on seizure foci locations within the frontal lobe.[19] Specifically, individuals with foci in primary motor regions have greater alterations in task-based and resting-state fMRI relative to controls than participants with foci in other frontal

lobe regions.[140] In the present study, individual seizure foci were identified for each participant; however, the number of participants was not sufficient to divide them into subgroups for further analysis.

4.3.2 Psychosocial Factors

It is well established that patients with epilepsy have higher rates of depression, anxiety disorders, and substance abuse than the general population.[139,141] Each of these comorbidities have been shown to alter resting-state networks,[142,143] as well as task-based activations,[142-144] when compared to controls. Most commonly, fMRI resting-state data exhibited decreased connectivity within specific networks,[145-147] and fMRI activation during specific tasks was either increased or supressed.[142-144,148] Participants in the present study were not excluded based on the presence of psychiatric comorbidities. Indeed, some participants had reported incidents of depression in years prior to the study, though none were actively reporting depressive symptoms. Previous studies have suggested that both resting-state and task-based data involving motor regions can be influenced by depressive symptoms. A study examining people diagnosed with depression using magnetoencephalography revealed asymmetry of the alpha band (8-12Hz) between the left and right rolandic areas at rest, suggesting an imbalance in resting-state connectivity.[149] Additionally, research using transcranial magnetic stimulation in patients with depression revealed less of a response to evoked stimulation of the finger.[150]

4.3.3 AEDs

Participants examined in our study were on various AEDs and drug regimens (monotherapy and polytherapy). Previous research examining the impact of AEDs on fMRI data has been mixed;

alterations in BOLD signals were observed in some studies, while other studies found no significant differences. Some of the major AEDs investigated included carbamazepine,[151-153] topiramate,[152,154,155] levetiracetam,[152] and lamotrigine.[153,156] Topiramate has been studied in patients with epilepsy during task-based fMRI. These studies indicated a dose-dependent reduction of cortical activity and connectivity within regions of all four lobes.[154,155] Topiramate has multiple mechanisms of action including enhancement of $GABA_A$ receptor activity, perhaps providing an explanation for the decreased activation.[154] Though examined less extensively, lamotrigine[156] and carbamazepine[151] have also been shown to cause an overall decrease in BOLD signal; both drugs act on voltage-gated sodium channels to prevent repetitive action potentials.[151,156]

Additional studies examining various mono- and polytherapies, as well as various drug-loads demonstrated little or no effects of AEDs on fMRI activation.[152,153,157] Specifically, unpublished data from our lab examined newly diagnosed patients with epilepsy before and after drug administration, and found no effect of carbamazepine, lamotrigine, valproate and phenytoin monotherapy on mean activation maps during a finger-tapping task.[153]

The variability in the results of these studies emphasizes the unknown effects of AEDs on the BOLD signal response. While their effects need to be addressed and considered, it is difficult to determine the consequences on the present study. The study examining sensorimotor activation demonstrated little to no difference in the BOLD signal as a result of AED use, reaffirming our results.[153] However, patients were only examined after 8-12 weeks of use of a single drug, while patients in the present study were being treated with mono- and polytherapy with various drugs and for differing time periods.

4.4 Future Directions

4.4.1 Pre-Surgical Predictions

Replacing direct cortical stimulation with task-based fMRI as the gold standard for pre-surgical motor mapping may be advantageous. FMRI has no known identified risks and has shown high concordance with direct cortical stimulation.[31] Additionally, motor mapping can be performed without exposing brain tissue and can therefore be easily repeated if necessary.

Research has facilitated the ability to retrospectively identify seizure foci using resting-state connectivity. Using resting-state connectivity to identify the seizure onset zone is beneficial because it can detect deep brain structures that are difficult to identify using scalp EEG. One study identified a region in the right thalamus whose connectivity to the hippocampi distinguished left from right TLE groups.[158] Further progress was demonstrated in patients with right or left mesial TLE, in whom lateralization was identified at an *individual* level by examining resting-state networks of five regions of interest.[76] Moreover, resting-state fMRI studies revealed that *precise* brain regions anti-correlated to the posterior cingulate were responsible for generating interictal discharges in patients with epilepsy.[159] In the present work, increasing the number of participants in the right and left FLE groups may reveal connectivity differences between the two. Additionally, studying more participants in each FLE subgroup (primary motor, supplementary sensorimotor, dorsolateral, orbitofrontal, anterior frontopolar, opercular, cingulate) would allow for comparisons between more defined frontal lobe regions, and thus more precise localization of seizure foci.

4.4.2 Post-Surgical Predictions

Task-based fMRI has been utilized to predict post-surgical functional deficits. Many studies have revealed that greater ipsilateral (to resection site) activation during verbal and memory task performance was correlated with greater post-surgical memory decline.[160-162] Unfortunately, these studies are highly dependent on task performance, which can introduce confounding variables into the results.

Task-dependent variability can be eliminated using resting-state connectivity, which has also been implemented to predict post-surgical functional deficits. In patients with TLE, functional connectivity was stronger between the hippocampus and superior temporal gyrus in patients who exhibited a post-surgical decline in verbal learning.[163] Additionally, one study was able to retrospectively and very robustly predict the extent of post-surgical memory deficits based on pre-surgical connectivity in resting-state memory networks.[77] Research in this area demonstrates the ability of resting-state connectivity to accurately predict post-surgical functional deficits. Accurate predictions of post-surgical outcomes would lead to more informed pre-surgical decisions for both patients and physicians.

4.5 Overall Conclusions

The present study provided insights into the disruption of motor networks in patients with FLE. The use of fMRI not only provided a non-invasive technique to examine these networks, but also did so at a high spatial resolution. This facilitated the discovery of changes in motor recruitment patterns during motor tasks and alterations in communication between motor regions at rest, findings that may help explain functional motor deficits experienced by patients with FLE during daily activities. This knowledge provides groundwork to continue exploration in a greater

number of individuals, and may eventually lead to the development of advantageous clinical procedures. Pre-surgical fMRI motor mapping is less invasive than the gold standard, direct cortical stimulation, and comparisons of cortical activation can easily be made over time in large groups of individuals. Additionally, resting-state connectivity is gaining headway in predicting post-surgical functional deficits, as well as localizing seizure onset zones. I hope that the implementation of such techniques will ultimately become standard procedure in the treatment of patients with FLE to further the treatment of this disabling disorder.

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